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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	4	OCT 28	KOREAPAT now available on STN
NEWS	5	NOV 30	PHAR reloaded with additional data
NEWS	6	DEC 01	LISA now available on STN
NEWS	7	DEC 09	12 databases to be removed from STN on December 31, 2004
NEWS	8	DEC 15	MEDLINE update schedule for December 2004
NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	JAN 11	CA/CAPLUS - Expanded patent coverage to include Russia (Federal Institute of Industrial Property)

NEWS EXPRESS	JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:04:05 ON 11 JAN 2005

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'REGISTRY' ENTERED AT 14:04:14 ON 11 JAN 2005
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STRUCTURE FILE UPDATES:     9 JAN 2005  HIGHEST RN 810659-29-1
DICTIONARY FILE UPDATES:    9 JAN 2005  HIGHEST RN 810659-29-1

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10622254.str
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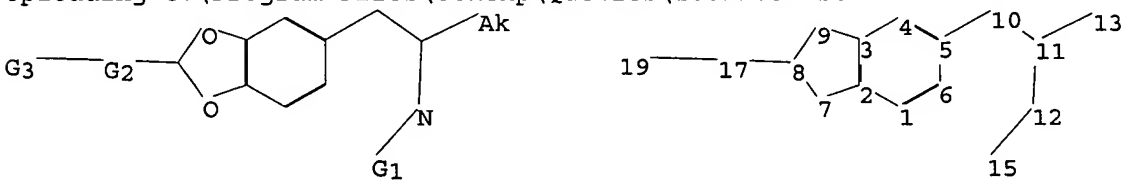


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chain nodes :
10  11  12  13  15  17  19
ring nodes :
1  2  3  4  5  6  7  8  9
chain bonds :
5-10  8-17  10-11  11-12  11-13  12-15  17-19
ring bonds :
1-2  1-6  2-3  2-7  3-4  3-9  4-5  5-6  7-8  8-9
exact/norm bonds :
8-17  11-12  11-13  12-15  17-19
exact bonds :
2-7  3-9  5-10  7-8  8-9  10-11
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6
isolated ring systems :
containing 1 :
```

G1:H,Ak

G2:CH2,C

G3:O,NH

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:CLASS
11:CLASS 12:CLASS 13:CLASS 15:CLASS 17:CLASS 19:CLASS

L1 STRUCTURE UPLOADED

=> s l1
SAMPLE SEARCH INITIATED 14:04:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 44 TO ITERATE

100.0% PROCESSED 44 ITERATIONS 22 ANSWERS
SEARCH TIME: 00.00.01

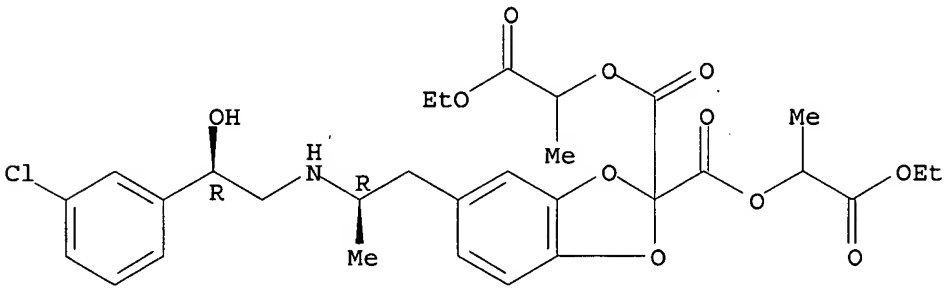
FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 483 TO 1277
PROJECTED ANSWERS: 159 TO 721

L2 22 SEA SSS SAM L1

=> d scan

L2 22 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(2-ethoxy-1-methyl-2-oxoethyl) ester, hydrochloride (9CI)
MF C30 H36 Cl N O11 . Cl H

Absolute stereochemistry.

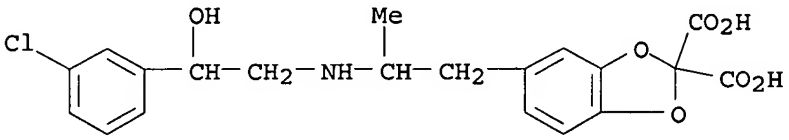


● HCl

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):4

L2 22 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN

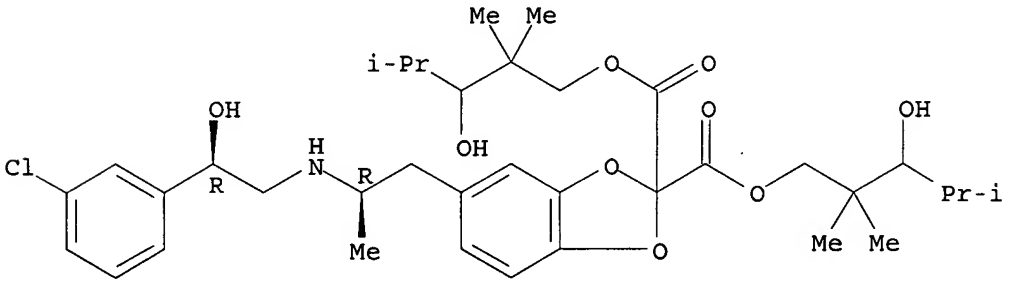
IN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI)
MF C20 H20 Cl N O7 . 2 Na



●2 Na

L2 22 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(3-hydroxy-2,2,4-trimethylpentyl) ester, hydrochloride (9CI)
MF C36 H52 Cl N O9 . Cl H

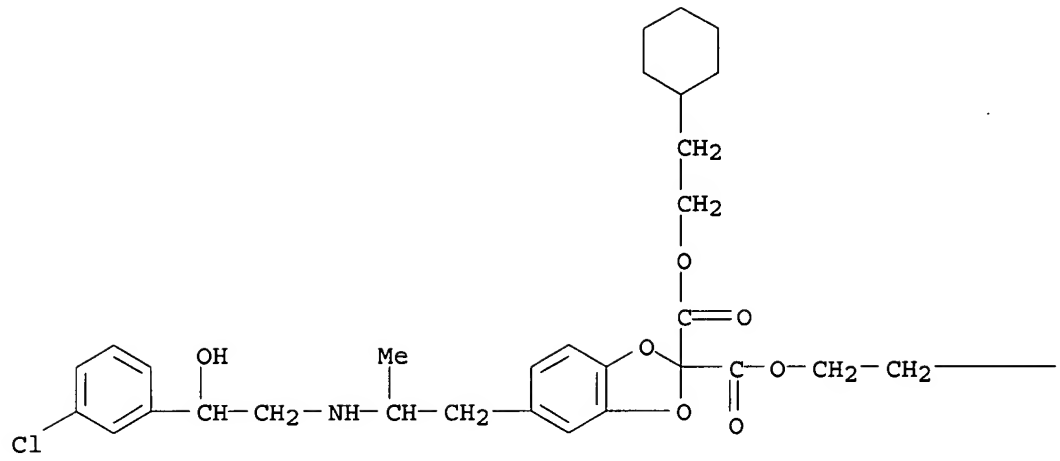
Absolute stereochemistry.



● HCl

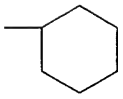
L2 22 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(2-cyclohexylethyl) ester, hydrochloride (9CI)
MF C36 H48 Cl N O7 . Cl H

PAGE 1-A



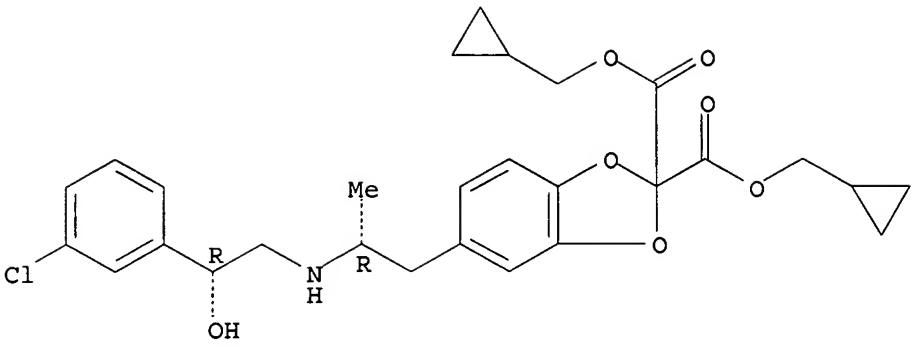
● HCl

PAGE 1-B



L2 22 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(cyclopropylmethyl) ester (9CI)
MF C28 H32 Cl N O7
CI COM

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):0

=> s l1 ful
FULL SEARCH INITIATED 14:06:01 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 769 TO ITERATE

100.0% PROCESSED 769 ITERATIONS 359 ANSWERS
SEARCH TIME: 00.00.01

L3 359 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	162.19	162.40

FILE 'CAPLUS' ENTERED AT 14:06:10 ON 11 JAN 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 11 Jan 2005 VOL 142 ISS 3
FILE LAST UPDATED: 10 Jan 2005 (20050110/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

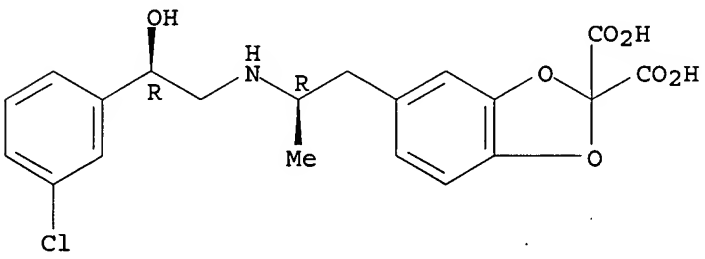
=> s l3
L4 167 L3

```
=> s l4 and antigen or hapten
        264674 ANTIGEN
        208091 ANTIGENS
        328367 ANTIGEN
                 (ANTIGEN OR ANTIGENS)
          9405 HAPTEN
          6341 HAPTENS
         11779 HAPTEN
                 (HAPTEN OR HAPTENS)
L5       11779 L4 AND ANTIGEN OR HAPTEN

=> d l4 ibib hitstr abs 1
```

L4 ANSWER 81 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:324884 CAPLUS
DOCUMENT NUMBER: 131:124801
TITLE: Development of beta3-adrenoceptor agonists for the treatment of obesity and diabetes - an update
AUTHOR(S): Weyer, C.; Gautier, J. F.; Danforth, E., Jr.
CORPORATE SOURCE: National Institutes of Health, Phoenix, AZ, 85016, USA
SOURCE: Diabetes & Metabolism (1999), 25(1), 11-21
CODEN: DIMEFW; ISSN: 1262-3636
PUBLISHER: Masson Editeur
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(development of beta3-adrenoceptor agonists for obesity and diabetes treatment)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB A review with 94 refs. Beta3-adrenoceptor (β3-AR) agonists were found to have remarkable anti-obesity and anti-diabetic effects in rodents shortly after their discovery in the early 1980s. Despite these promising qualities, several pharmaceutical problems and theor. concerns have slowed

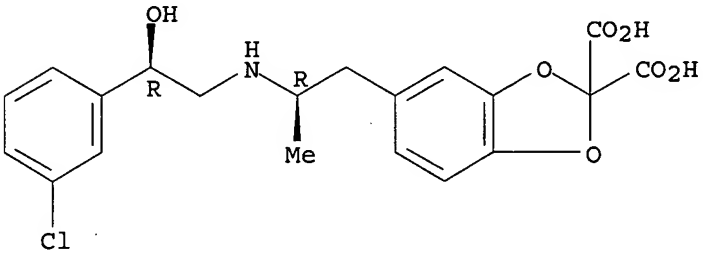
the development of these products as therapeutic agents in humans during the last 15 yr. To date, the pharmaceutical industry has not been successful in developing a β3-AR agonist for use in the treatment of human obesity and type 2 diabetes. Pharmaceutical problems in this area concern important differences between rodent and human β3-AR and the difficulty in finding a compound with sufficient bioavailability that is a highly selective and full agonist at the human receptor. Some of these problems seem to have been solved with the cloning of the human β3-AR, which has made it possible to develop novel compds. directly and specifically against the human receptor. However, several theor. concerns still remain. These include the major question as to whether the number of biol. active β3-ARs in adult humans is sufficient to produce relevant metabolic effects and, if so, whether their long-term stimulation is safe and free of unwarranted side effects. In addition, the mechanisms of action of β3-AR agonists remain poorly understood. Recent studies using CL 316,243, a highly selective β3-adrenergic compound, have provided new insights into the potential mechanisms of action of these drugs in rodents as well as the first evidence that treatment with a highly selective β3-AR agonist exerts relevant metabolic effects in humans. It appears that chronic β3-adrenergic stimulation in white adipose tissue increases the expression of newly discovered mitochondrial uncoupling proteins (UCP 2 and 3) and a "reawakening" of dormant brown adipocytes. In addition, β3-ARs may be present in skeletal muscle where ectopic expression of UCP-1 has been reported. If these findings are confirmed, tissues other than brown fat may play an important role in mediating β3-adrenergic effects on thermogenesis and substrate oxidation In humans, treatment with CL 316,243 for 8 wk, in spite of limited bioavailability, induced marked plasma concentration-dependent increases in insulin sensitivity, lipolysis, and fat oxidation in lean volunteers, without causing β1-, or β2-mediated side effects. These results clearly indicate that favorable metabolic effects can be achieved by selective β3-AR stimulation in humans. The compds. of the next generation currently emerging from preclin. development are full agonists at the human β3-AR. These agents have demonstrated promising results in non-human primates. It will be interesting to see whether their efficacy in clin. trials is superior to that achieved with previous (rodent) β3-AR agonists and, if so, whether their effects will eventually translate into weight loss and improved metabolic control that could facilitate their use as effective drugs for the treatment of obesity and Type 2 diabetes in humans.

REFERENCE COUNT: 94 THERE ARE 94 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 82 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:230235 CAPLUS
DOCUMENT NUMBER: 130:292080
TITLE: Vitamin A and β3 adrenergic regulation of leptin and UCP1 expression: role in energy homeostasis and senescence
AUTHOR(S): Kumar, Monica Vivek
CORPORATE SOURCE: Univ. of Florida, Gainesville, FL, USA
SOURCE: (1998) 123 pp. Avail.: UMI, Order No. DA9905977 From: Diss. Abstr. Int., B 1999, 59(9), 4747
DOCUMENT TYPE: Dissertation
LANGUAGE: English
IT **138908-40-4**, CL316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vitamin A and β3 adrenergic regulation of leptin and UCP1

expression in energy homeostasis and senescence)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

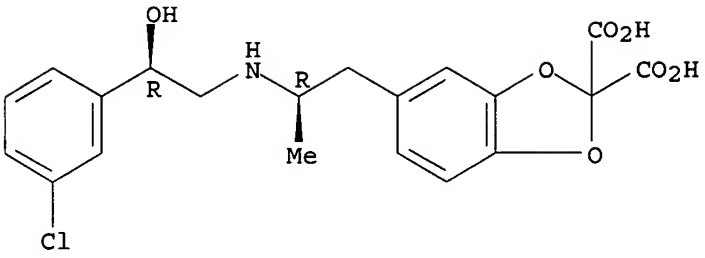


●2 Na

AB Unavailable

L4 ANSWER 83 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:208389 CAPLUS
DOCUMENT NUMBER: 131:14328
TITLE: Acute and chronic regulation of ob mRNA levels by β3-adrenoceptor agonists in obese yellow KK mice
AUTHOR(S): Sakane, Naoki; Yoshida, Toshihide; Umekawa, Tsunekazu; Kogure, Akinori; Kondo, Motoharu; Nakamura, Yoshiko; Sasaki, Yasunori; Asano, Atsushi; Saito, Masayuki
CORPORATE SOURCE: First Department of Internal Medicine, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan
SOURCE: Endocrine Journal (Tokyo) (1998), 45(5), 647-651
CODEN: ENJOEO; ISSN: 0918-8959
PUBLISHER: Japan Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(β3-adrenoceptor agonist effect on ob gene expression in adipose tissue of obese yellow KK mice)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

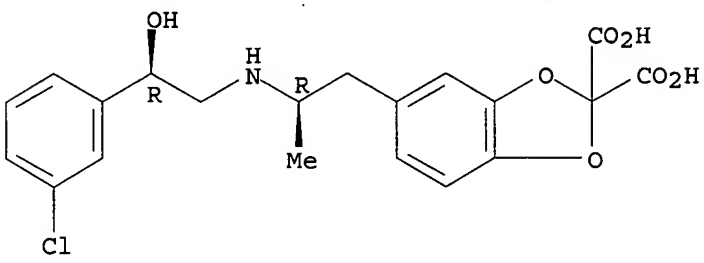
AB The inhibitory effect of β3-adrenoceptor agonists on the ob gene in brown adipose tissue (BAT) and white adipose tissue (WAT) is now well documented both in vivo in lean animals and in vitro, but the reported effects of β3-adrenoceptor agonists on ob gene expression in obese animals remain controversial. The authors investigated whether ob gene (leptin) expression in BAT and WAT is reduced by acute and chronic administrations of a β3-adrenoceptor agonist, CL316,243 (CL). The ob gene mRNA levels in BAT, perimetric and inguinal WAT of obese Yellow KK mice were about 4-fold higher than those of lean controls. Acute exposure (6 h) to CL decreased ob gene mRNA levels in three fat depots in both animals. Chronic exposure (10 days) to CL also decreased ob gene mRNA levels in BAT, perimetric, and inguinal WAT in both animals. The authors concluded that acute and chronic regulation by a β3-adrenoceptor agonist suppressed ob gene expression in obese Yellow KK mice and lean controls.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 84 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:197227 CAPLUS
DOCUMENT NUMBER: 130:347731
TITLE: Stimulation of the extracellular signal-regulated kinase 1/2 pathway by human beta-3 adrenergic receptor: new pharmacological profile and mechanism of activation
AUTHOR(S): Gerhardt, C. C.; Gros, J.; Strosberg, A. D.; Issad, T.
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire, Centre National de la Recherche Scientifique, Laboratoire d'Immuno-Pharmacologie Moleculaire, Universite Paris VII, Paris, Fr.
SOURCE: Molecular Pharmacology (1999), 55(2), 255-262
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(extracellular signal-regulated kinase 1/2 pathway stimulation by human β3-adrenergic receptor and pharmacol. profile and mechanism of activation thereof)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-

chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB We present evidence that stimulation of the human beta-3 adrenergic receptor (AR), expressed in Chinese hamster ovary/K1 cells, specifically activates the mitogen-activated protein kinases extracellular signal-regulated kinase (ERK)1 and 2, but not JNK or p38. The extent and kinetics of the ERK stimulation by the beta-3 AR are identical with those of the endogenic insulin receptor. However, insulin augments cellular proliferation, whereas beta-3 AR agonists inhibit proliferation due to the production of cAMP. The pharmacol. profile of the ERK activation by the beta-3 AR differs significantly from its activation of adenylyl cyclase. The order of potency and intrinsic activities of both natural ligands, norepinephrine and epinephrine, is inversed between both signaling pathways. In addition, BRL 37344 and propranolol, ligands that act as agonists in the stimulation of cyclase, act as antagonists for ERK activation. The activation of ERK1/2 is sensitive to pertussis toxin, suggesting that the beta-3 AR, in addition to its interaction with Gs, can couple to Gi/o. Furthermore, the activation of ERK by the beta-3 AR is sensitive to PD 98059, wortmannin, and LY 294002, indicating a crucial role for mitogen-activated protein kinase and phosphatidylinositol-3 kinase (PI3K), resp. A beta-3 AR-mediated stimulation of PI3K is confirmed by the observation that the selective agonist CGP 12177A specifically activates protein kinase B. As was observed for the activation of ERK, the activation of protein kinase B is inhibited by preincubation with pertussis toxin and PI3K inhibitors, suggesting that both are a consequence of a Gi/o-mediated activation of PI3K.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 85 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:188533 CAPLUS
DOCUMENT NUMBER: 131:448
TITLE: Aryl propanolamines: comparison of activity at human β3 receptors, rat β3 receptors and rat atrial receptors mediating tachycardia
AUTHOR(S): Cohen, Marlene L.; Bloomquist, William; Kriauciunas, Aidas; Shuker, Anthony; Calligaro, David
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: British Journal of Pharmacology (1999), 126(4), 1018-1024
CODEN: BJPCBM; ISSN: 0007-1188

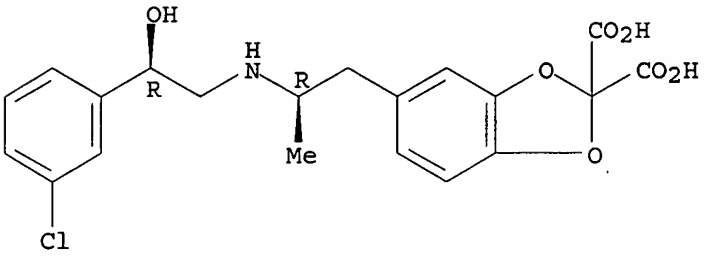
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **138908-40-4**, CL316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aryl propanolamines: comparison of activity at human β3 receptors, rat β3 receptors and rat atrial receptors mediating tachycardia)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



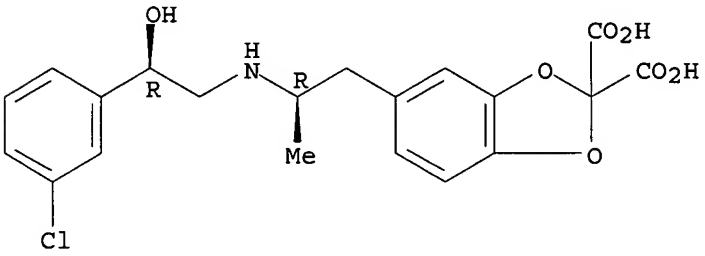
●2 Na

AB The in vitro activity of 4 aryl propanolamines was compared to 2 prototypic β3 receptor agonists, CGP 12177 and CL316243 at the human β3 receptor, the rat β3 receptor in the stomach fundus and receptors mediating atrial tachycardia. L-739,574 was the most potent (EC50 = 9 nM) and selective agonist at the human β3 receptor with high maximal response (74% of the maximal response to isoproterenol). A phenol-biaryl ether analog possessed modest affinity for the human β3 receptor (EC50 = 246 nM), but was highly efficacious with a maximal response 82% of the maximal response to isoproterenol. The other derivs. were intermediate in potency with low maximal responses. These agonists at the human β3 receptor did not activate the rat β3 receptor in the rat stomach fundus. In fact, the aryl propanolamines (10-6 M) inhibited CL316243-induced activation of the rat β3 receptor. Thus, agonist activity at the human β3 receptor translated into antagonist activity at the rat β3 receptor. L739,574 and the phenol biaryl ether increased heart rate via β1 receptors. Although CGP 12177 produced atrial tachycardia, neither the indole sulfonamide nor biphenyl biaryl ether did, although both had high affinity for the human β3 receptor. Thus, the atrial tachycardic receptor was not identical to the human β3 receptor. These studies (a) characterized 4 aryl propanolamines with high affinity at the human β3 receptor, (b) found that they were antagonists at the rat β3 receptor, an observation with profound implications for in vivo rat data, and (c) established that the rodent atrial non-β1, β2, or β3 tachycardic receptor was also unrelated to the human β3 receptor.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 106 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:751676 CAPLUS
DOCUMENT NUMBER: 128:84320
TITLE: Lipolytic effects of conventional β3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells: preliminary pharmacological evidence for a putative β4-adrenoceptor
AUTHOR(S): Galitzky, Jean; Langin, Dominique; Verwaerde, Patrick; Montastruc, Jean-Louis; Lafontan, Max; Berlan, Michel
CORPORATE SOURCE: Laboratoire de Pharmacologie Medicale et Clinique, Unite 317 Institut National de la Sante et de la Recherche Medicale, Faculte de Medecine, Universite Paul Sabatier, Toulouse, 31073, Fr.
SOURCE: British Journal of Pharmacology (1997), 122(6), 1244-1250
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(lipolytic effects of conventional β3-adrenoceptor agonists and of CGP 12,177 in rat and human fat cells and evidence for a putative β4-adrenoceptor)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

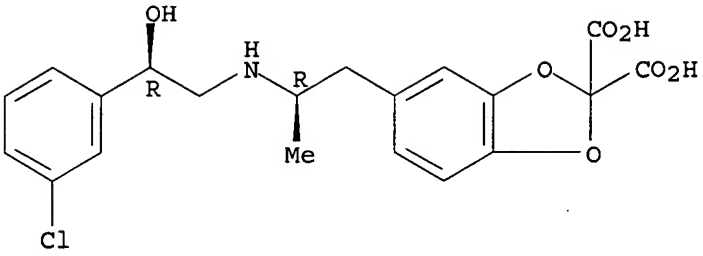
AB The nature of rat and human fat cell β3-adrenoceptors was investigated by studying the effects of the new β3-adrenoceptor selective antagonist, SR 59,230A, on lipolysis induced by the conventional β3-adrenoceptor agonists, CL 316,243 and SR 58,611A, and by the non-conventional partial β3-adrenoceptor agonist CGP 12,177 (a potent β1- and β2-adrenoceptor antagonist with partial β3-adrenoceptor agonist property). In rat fat cells, the rank order of potency of agonists was: CL 316,243 > isoprenaline > SR 58,611A > CGP 12,177. The three former agents were full agonists whereas CGP 12,177 was a partial agonist (intrinsic activity of 0.70). In human fat cells, the lipolytic effect of CGP 12,177 reached 25 % of isoprenaline effect. CL

316,243 was a poor inducer of lipolysis and SR 58,611A was ineffective. In rat fat cells, lipolysis induced by CL 316,243 and SR 58,611A was competitively antagonized by SR 59,230A. Schild plots were linear with pA2 values of 6.89 and 6.37, resp. Conversely, 0.1, 0.5 and 1 μM SR 59,230A did not modify the concentration-response curve of CGP 12,177. A rightward shift of the curve was however observed with 10 and 100 μM of SR 59,230A. The apparent pA2 value was 5.65. The non-selective β-adrenergic antagonist, bupranolol, competitively displaced the concentration-response curve of CGP 12,177 and CL 316,243. Schild plots were linear with pA2 values of 6.70 and 7.59, resp. CL316,243-mediated lipolytic effect was not antagonized by CGP 20,712A. In human fat cells, CGP 12,177-mediated lipolytic effect was antagonized by bupranolol and CGP 20,712A. SR 59,230A (0.1, 1 and 10 μM) did not modify the concentration-response curve of CGP 12,177. A rightward shift was however observed at 100 μM leading to an apparent pA2 value of 4.32. The results suggest that the non-conventional partial agonist CGP 12,177 can activate lipolysis in fat cells through the interaction with a β-adrenoceptor pharmacol. distinct from the β3-adrenoceptor, i.e. through a putative β4-adrenoceptor. They suggest that the two subtypes coexist in rat fat cells whereas only the putative β4-adrenoceptor mediates lipolytic effect of CGP 12,177 in human fat cells.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 107 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:720849 CAPLUS
DOCUMENT NUMBER: 128:10554
TITLE: Role of β1- and β3-adrenoceptors in the regulation of lipolysis and thermogenesis in rat brown adipocytes
AUTHOR(S): Atgie, Claude; D'Allaire, Francois; Bukowiecki, Ludwik J.
CORPORATE SOURCE: Dep. Physiol., Fac. Med., Laval Univ., Quebec, QC, G1K 7P4, Can.
SOURCE: American Journal of Physiology (1997), 273(4, Pt. 1), C1136-C1142
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL-316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(β1- and β3-adrenoceptors in regulation of lipolysis and thermogenesis in rat brown adipocytes)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

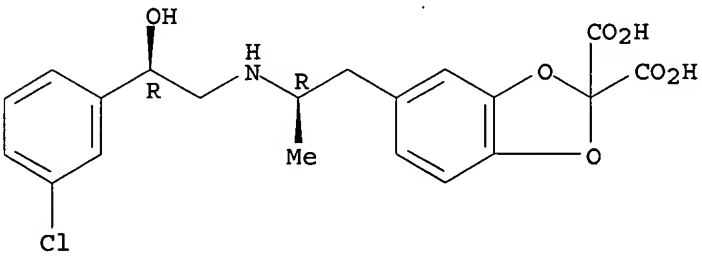
AB To evaluate the physiol. functions of β1-, β2-, and β3-adrenoceptors (ARs) in brown adipose tissue, the lipolytic and respiratory effects of various adrenergic agonists and antagonists were studied in rat brown adipocytes. The β-agonists stimulated both lipolysis and respiration (8-10 times above basal levels), with the following order of potency (concentration eliciting 50% of maximum response): CL-316243 (β3) > BRL-37344 (β3) > isoproterenol (mainly β1/β2) > norepinephrine (NE; mainly β1/β2) > epinephrine (mainly β1/β2) » dobutamine (β1) » procaterol (β2). Schild plot coeffs. of competitive inhibition expts. using ICI-89406 (β1 antagonist) revealed that more than one type of receptor mediates NE action. It is concluded from our results that (1) NE, at low plasma levels (1-25 nM), stimulates lipolysis and respiration mainly through β1-ARs, (2) NE, at higher levels, stimulates lipolysis and respiration via both β1- and β3-ARs, (3) β2-ARs play only a minor role, and (4) β3-ARs may represent the physiol. receptors for the high NE concns. in the synaptic cleft, where the high-affinity β1-ARs are presumably desensitized. It is also suggested that lipolysis represents the flux-generating step regulating mitochondrial respiration.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 108 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:583799 CAPLUS
DOCUMENT NUMBER: 127:303164
TITLE: Thiazolidinediones inhibit alkaline phosphatase activity while increasing expression of uncoupling protein, deiodinase, and increasing mitochondrial mass in C3H10T1/2 cells
AUTHOR(S): Paulik, Mark A.; Lenhard, James M.
CORPORATE SOURCE: Department of Metabolic Diseases, Glaxo Wellcome Inc., Research Triangle Park, NC, 27709, USA
SOURCE: Cell and Tissue Research (1997), 290(1), 79-87
CODEN: CTSRCS; ISSN: 0302-766X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(thiazolidinedione inhibition of alkaline phosphatase activity while increasing expression of uncoupling protein, deiodinase, and increasing mitochondrial mass in C3H10T1/2 cells)

RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB Although there are a number of cell lines committed to differentiate into brown adipocytes, the stem-cell origin of brown fat remains unclear. To address this problem, we explored the effects of various pharmacol. agents on differentiation of C3H10T1/2 cells, a pluripotent stem-cell line of mesodermal origin. Histochem. and biochem. anal. revealed that, when these cells were treated with retinoic acid, they expressed the osteoblastic marker alkaline phosphatase. Upon addition of thiazolidinediones and insulin, these cells accumulated lipid and expressed the adipocyte marker aP2, indicating differentiation into adipocytes. Treatment during the growth phase with thiazolidinediones resulted in maximal lipogenesis indicating a need for clonal expansion for efficient adipogenic differentiation. Further anal. revealed that addition of thiazolidinediones to the cells increased (1) the lipolytic response of the cells to β3-agonists, (2) the expression of uncoupling protein (UCP), (3) the expression of mRNA for type II iodothyronine 5'-deiodinase (5'D-II), and (4) mitochondrial staining. These results suggest the anti-diabetic effects of thiazolidinediones may, in part, involve increased brown adipocyte differentiation. Moreover, this is the first direct evidence indicating that brown adipocytes and osteoblasts may arise from the same stem cell.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

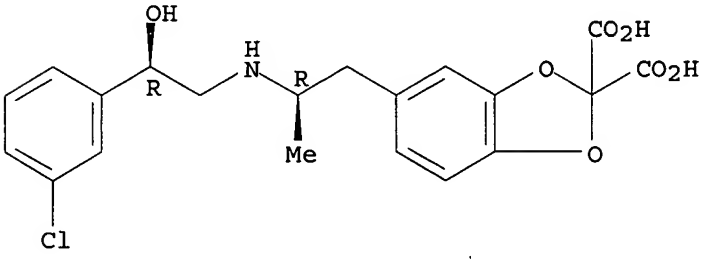
L4 ANSWER 109 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:564311 CAPLUS
DOCUMENT NUMBER: 127:214966
TITLE: Effects of thiazolidines on adipose tissue of Zucker fatty rat
AUTHOR(S): Okuno, Akira; Tamemoto, Hiroyuki; Ueki, Kojiro; Tobe, Kazuyuki; Kadowaki, Takashi; Yazaki, Yoshio; Akanuma, Yasuo; Horikoshi, Hiroyoshi
CORPORATE SOURCE: Dai 3 Naika, Tokyo Daigaku, Tokyo, 113, Japan
SOURCE: Diabetes Frontier (1997), 8(4), 499-501
CODEN: DIFREZ; ISSN: 0915-6593
PUBLISHER: Medikaru Rebyusha
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
IT **138908-40-4**, CL316243

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects of troglitazone on adipose tissue of Zucker fatty rat)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB Zucker fatty rats (ZFRs) and Zucker lean rats (ZLRs) were fed on a diet containing 0.2% troglitazone (TR) alone, 0.001% CL316243 (CL) alone (a β-adrenoceptor agonist), or 0.2% TR + 0.001% CL for 3-4 wk. TR increased wet wts. of the interscapular brown adipose tissue (BAT) by 1.3 times in ZLRs and 2.5 times in ZFRs. Total triglyceride contents in BAT were increased in proportion to TR increases. CL completely inhibited the TR-induced increase in BAT wts. in ZFRs. MRNA expression levels of uncoupling protein (UCP) and β3-adrenoceptor (β3AR) in ZFRs were significantly lower than those in ZLRs. TR increased UCP mRNA expression level in ZFRs to the same level in ZLRs. CL increased the UCP mRNA expression level more markedly than TR though it decreased β3AR mRNA expression level. TR did not affect wet wts. of white adipose tissue (WAT) and mRNA expression of peroxisome proliferator-activated receptor-γ (PPRAγ) in both ZFRs and ZLRs. TR normalized the increased expression levels of tumor necrosis factor α mRNA in visceral adipose tissues and leptin mRNA in almost all the adipose tissues except the adipose tissue surrounding the epididymis of ZFRs. TR increased total DNA contents in WAT of ZFRs. Histol. examination revealed that a mass of small size fat cells was found sporadically in WAT of ZFRs treated with TR. These results suggest that thiazolidines possibly improve insulin resistance associated with obesity.

L4 ANSWER 150 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:452620 CAPLUS

DOCUMENT NUMBER: 122:205683

TITLE: Effect of CL 316,243, a novel β3-adrenoceptor agonist, on insulin secretion in perfused mouse pancreas

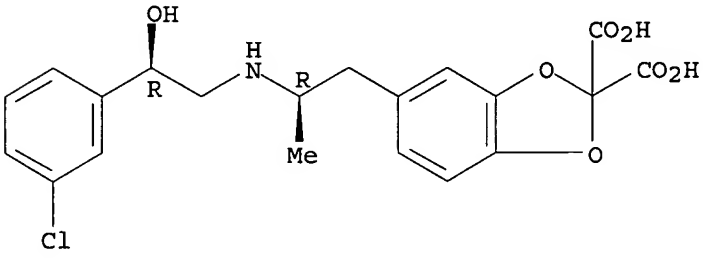
AUTHOR(S): Yoshida, Toshihide; Yoshioka, Keiji; Hiraoka, Noriya; Umekawa, Tsunekazu; Sakane, Naoki; Kondo, Motoharu

CORPORATE SOURCE: First Department of Internal Medicine, University of Medicine, Kyoto, 602, Japan

SOURCE: Endocrine Journal (Kyoto, Japan) (1994), 41(6), 671-5

CODEN: ENJOEO; ISSN: 0918-8959
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(effect of CL 316,243, a novel β3-adrenoceptor agonist, on insulin secretion in perfused mouse pancreas)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB To clarify the insulin-release mechanism of β3-adrenoceptor agonists, the authors examined the effect of CL 316,243, a highly specific β3-adrenoceptor agonist having a relative potency of β1:β2:β3 = 0:1:100,000, on insulin secretion in perfused mouse pancreas. The application of 0.2 mM and 0.5 mM CL 316,243 produced significant insulin secretion from within 1 min, which lasted until 2 min after its withdrawal. D,L-Propranolol and ICI 118551 at 0.2 mM partially inhibited the insulin secretion induced by the 0.2 mM CL 316,243, but 0.2 mM metoprolol had no effect on the insulin release produced by 0.2 mM CL 316,243. The authors conclude that β3-adrenoceptor agonist stimulates insulin secretion via β3-action in the perfused mouse pancreas.

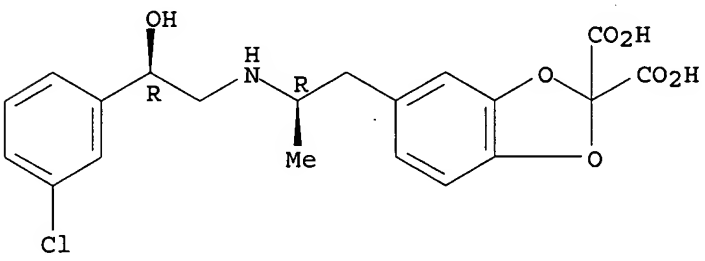
L4 ANSWER 151 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:411448 CAPLUS
DOCUMENT NUMBER: 122:179271
TITLE: Apparent lack of β3-adrenoceptors and of insulin regulation of glucose transport in brown adipose tissue of guinea pigs
AUTHOR(S): Himms-Hagen, Jean; Triandafillou, Joan; Begin-Heick, Nicole; Ghorbani, Masoud; Kates, Anna-Lisa
CORPORATE SOURCE: Dep. Biochem., Univ. Ottawa, Ottawa, ON, K1H 8M5, Can.
SOURCE: American Journal of Physiology (1995), 268(1, Pt. 2), R98-R104
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); BIOL (Biological study)
(β3-adrenoceptors and insulin effect on glucose transport in brown adipose tissue in cold acclimation in guinea pig)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB Norepinephrine-induced thermogenesis was substantial in adipocytes from brown adipose tissue (BAT) of cold-acclimated guinea pigs but absent in adipocytes from BAT of warm-acclimated guinea pigs. There was no thermogenic response to any β3-adrenergic agonist (CL-316,243, ZD-7114, BRL-28410, CGP-12177). The receptor was characterized as a β1-adrenoceptor. Adrenergic agonists stimulated adenylate cyclase in membranes from BAT of both warm- and cold-acclimated guinea pigs also via a β1-adrenoceptor; β3-adrenergic agonists had no effect. Glucose transport by brown adipocytes from warm-acclimated guinea pigs was not stimulated by either norepinephrine or insulin. Cold acclimation induced the appearance of stimulation of glucose transport by norepinephrine in association with the appearance of a large capacity for thermogenesis, but there was little improvement in response to insulin. GLUT4 was present in membranes from BAT of both warm- and cold-acclimated guinea pigs. Insulin is known to have an antilipolytic effect on both BAT and white adipose tissue of guinea pigs. Thus there is a selective lack of insulin-regulated glucose transport that is not improved by cold acclimation. Guinea pigs may have a mutated component of the translocation mechanism for GLUT4. β3-Adrenoceptors appear to be absent in brown adipocytes of adult guinea pigs, as in white adipocytes of guinea pigs, yet are known to be present in the gut. Tissue-specific expression of β3-adrenergic receptors in guinea pigs may differ from that in rats, in which receptors are expressed in the adipose tissues and gut.

L4 ANSWER 152 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:352451 CAPLUS

DOCUMENT NUMBER: 122:151975

TITLE: β2-Adrenoceptors mediate a reduction in endothelial permeability in vitro

AUTHOR(S): Allen, Michael J.; Coleman, Robert A.

CORPORATE SOURCE: Department of Pharmacology 1, Glaxo Research and Development Ltd., Park Road, Ware Herts, SG12 0DP, UK

SOURCE: European Journal of Pharmacology (1995), 274(1-3), 7-15

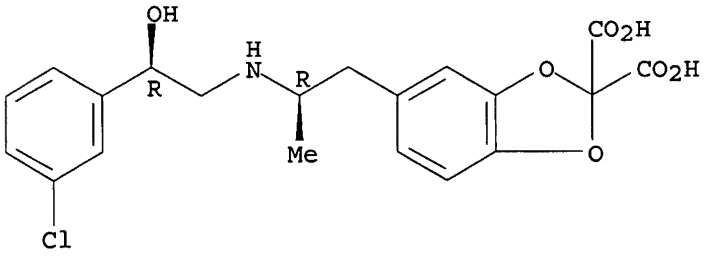
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **138908-40-4**, CL-316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(adrenoceptors in mediation of endothelial permeability in vitro)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

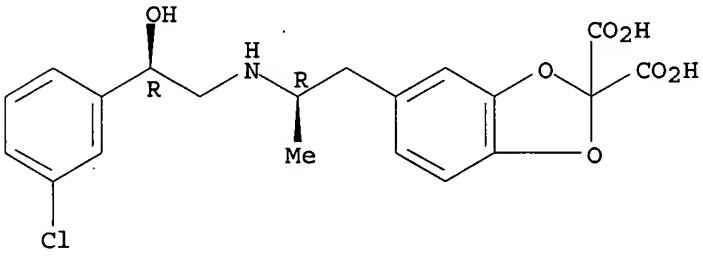


AB The permeability of bovine pulmonary artery endothelial (CPAE) monolayers to Evans blue-labeled albumin (Evans blue-albumin) has been measured in vitro. Thrombin caused a concentration-dependent increase in Evans blue-albumin clearance across endothelial monolayers. Isoprenaline inhibited thrombin-induced Evans blue-albumin clearance in a concentration-dependent manner (EC50 21 nM). This effect was mimicked by the selective β2-adrenoceptor agonists salbutamol (EC50 64 nM) and salmeterol (EC50 2.7 nM), but not by the selective β1-adrenoceptor agonist, RO-363 ((1-[3',4'-dihydroxyphenoxy]-2-hydroxy- [3'',4''-dimethoxyphenethylamino]-propane)oxalate), nor by the selective β3-adrenoceptor agonist, CL-316,243 (disodium (R,R)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate). Isoprenaline, salbutamol and salmeterol, but not RO-363 or CL-316,243 produced small, but significant redns. in Evans blue-albumin clearance across unstimulated endothelial monolayers. Inhibition of the response to thrombin by isoprenaline was antagonized by the selective β2-adrenoceptor antagonist, ICI-118,551 ((erythro-DL-1(7-methylindan-4-yloxy)3-isopropylaminobutan-2-ol), pKB 8.4). Salmeterol also inhibited hydrogen peroxide-stimulated Evans blue-albumin clearance. Hence, the widely used β2-adrenoceptor agonists, salbutamol and salmeterol, are able to reduce endothelial permeability at nanomolar concns.

L4 ANSWER 153 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:329636 CAPLUS
DOCUMENT NUMBER: 122:97047
TITLE: Characterization of β1- and β3-adrenoceptors in intact brown adipocytes of the rat

AUTHOR(S): D'Allaire, Francois; Atgie, Claude; Mauriege, Pascale; Simard, Pierre-Michel; Bukowiecki, Ludwik Jan
CORPORATE SOURCE: Fac. Med., Laval Univ., QC, G1K 7P4, Can.
SOURCE: British Journal of Pharmacology (1995), 114(2), 275-82
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(β1- and β3-adrenoceptors in intact brown adipocytes of the rat)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB The binding properties of β1-, β2- and β3-adrenoceptors were determined in isolated brown adipocytes of the rat rather than in membrane prepns. from tissue homogenates, because typical brown adipocytes represent only about 40% of the various cells present in brown adipose tissue. Binding characteristics were assessed with the hydrophilic β-adrenoceptor radioligand, (-)-[3H]-CGP 12177. The potent β-antagonist, bupranolol (100 μM) was used to determine nonspecific binding. Characterization was essentially performed by saturation and competition studies. The saturation curve of (-)-[3H]-CGP 12177 was clearly biphasic (Hill coefficient, nH = 0.57) indicating the presence of two different β-adrenoceptor populations of high (KD = 0.24 nM) and low (KD = 80 nM) affinity. The low affinity sites were more numerous (Bmax = 121,000,000 sites/cell) than the high affinity sites (Bmax = 12,000 sites/cell). (-)-[3H]-CGP 12177 (25 nM) was displaced by adrenaline (Ad), noradrenaline (NA), isoprenaline (Iso), phenylephrine (Phe) and by the new β3 agonist, CL 316,243 (CL) in a biphasic pattern. The order of potency for (-)-[3H]-CGP 12177 displacement from the small population of high affinity sites (Iso » NA > Ad » CL » Phe) was in agreement with a β1/β2-classification. In contrast, the potencies of the same agonists for displacing the radioligand from the low affinity binding sites (CL » Iso > NA > Ad » Phe) revealed the presence of a distinct population of adrenoceptors obeying a β3-classification. 5-HT did not displace (-)-[3H]-CGP 12177 (25 nM) when used at concns. as high as 0.1 nM. The β-adrenoceptor antagonist, (-)-bupranolol, was more effective than (-)-propranolol for

displacing (-)-[3H]-CGP 12177 (25 nM) from the high (Ki = 0.029 and 0.19 nM, resp.) and low (Ki = 0.27 μM and 1.6 μM, resp.) affinity binding sites. The selective β1-antagonist CGP 20712A efficiently displaced the radioligand from a small population (Ki = 65 pM) of binding sites, confirming the presence of β1-adrenoceptors. To evaluate whether β2-adrenoceptors could be identified in the population of high affinity binding sites, displacement studies were performed at a low concentration of (-)-[3H]-CGP 12177 (4 nM) that mainly labeled β1/β2-adrenoceptors. ICI 118 551 (a selective β2-antagonist) and procaterol (a selective β2-agonist) displaced (-)-[3H]-CGP 12177 from its binding sites with very low affinity (Ki = 0.17 μM and K1 = 11 μM resp.). From these observations, the authors conclude that: (1) two kinds of binding sites with low and high affinities for (-)-[3H]-CGP 12177 can be detected in intact brown adipocytes, (2) there are 10 times more low than high affinity β-adrenoceptors, as determined by saturation or competition curve anal., (3) the high affinity binding sites mainly correspond to β1-adrenoceptors, whereas the low affinity sites represent β3-adrenoceptors, and (4) β2-adrenoceptors are undetectable. It is suggested that the low affinity β3-adrenoceptors represent the physiol. receptors for noradrenaline secreted from sympathetic nerve endings when the concentration of the neurohormone in the synaptic cleft is very high and/or when the high affinity β1-adrenoceptors are desensitized by prolonged sympathetic stimulation such as chronic cold exposure.

L4 ANSWER 154 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:312699 CAPLUS
DOCUMENT NUMBER: 122:96519
TITLE: β3-Adrenergic agonists for prevention and treatment of ulcer
INVENTOR(S): Yamaguchi, Isamu; Kodama, Hiroshi; Kuratani, Kazuyoshi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 06293664	A2	19941021	JP 1993-78327	19930405

PRIORITY APPLN. INFO.: JP 1993-78327 19930405

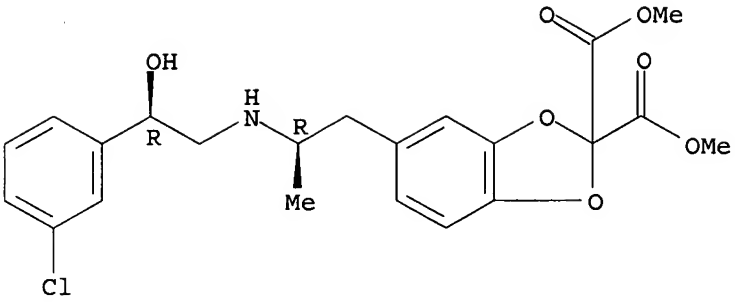
IT **160784-48-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phenethylamines as β3-adrenergic agonists and ulcer inhibitors)

RN 160784-48-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, [R-(R*,R*)]-, ethanedioate (2:1) (salt) (9CI) (CA INDEX NAME)

CM 1

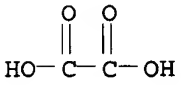
CRN 139012-91-2
CMF C22 H24 Cl N O7

Absolute stereochemistry.

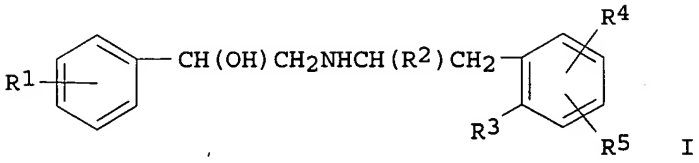


CM 2

CRN 144-62-7
CMF C2 H2 O4



GI



AB β3-Adrenergic agonists, e.g. phenethylamines I (R1 = halo; R2 = lower alkyl; R3 = H; R2R3 may form lower alkylene; R4 = (esterified) carboxy-substituted lower alkoxy; R5 = H; R4R5 may form (esterified) carboxy-substituted lower alkylenedioxy) or their pharmacol. acceptable salts are useful for prevention and treatment of ulcer. (R*,R*)-(±)-[4-[2-[2-(3-chlorophenyl)-2-hydroxyethylamino]propyl]phenoxy]acetic acid Me ester HBr salt inhibited indomethacin-induced ulcer with ED50 of 0.03 mg/kg in rats.

L4 ANSWER 155 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:310977 CAPLUS
DOCUMENT NUMBER: 122:123727
TITLE: Is the "atypical" β-receptor in the rat stomach fundus the rat β3 receptor?
AUTHOR(S): Cohen, Marlene L.; Granneman, James G.; Chaudhry, Archana; Schenck, Kathryn W.; Cushing, Daniel J.; Palkowitz, Alan D.
CORPORATE SOURCE: Lilly Res. Lab., Lilly Corporate Center, Indianapolis, IN, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1995), 272(1), 446-51
CODEN: JPETAB; ISSN: 0022-3565

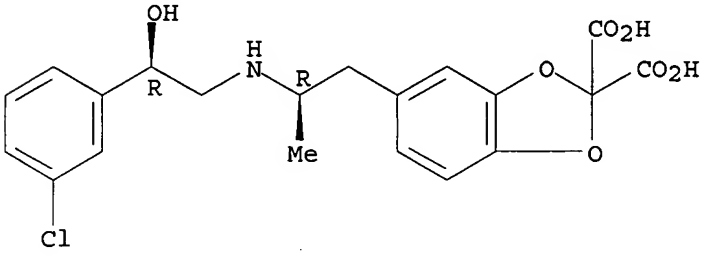
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(β3-adrenergic receptor in stomach fundus specificity for)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



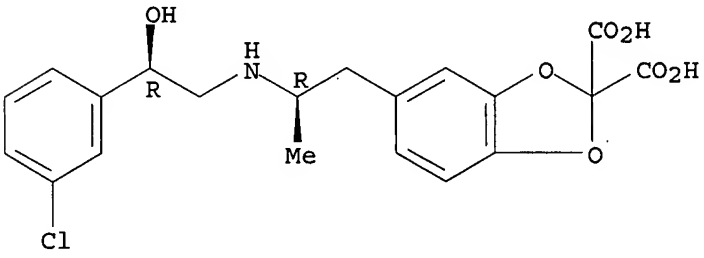
●2 Na

AB The rat gastric fundus is known to possess an "atypical" β-adrenergic receptor that mediates relaxation to isoproterenol. The purpose of this study was to characterize the relationship between this "atypical" β receptor in the rat stomach and the cloned rat β3 receptor by taking advantage of highly selective pharmacol. and mol. biol. probes of the β3 receptor. Nuclease protection anal. of RNA from the rat gastric fundus identified β3 receptor mRNA whose levels in the stomach were exceeded only by those in adipose tissue. Pharmacol. anal. of the recombinant rat β3 receptor expressed in Chinese hamster ovary cells indicated low affinity of propranolol with a Ki value of 2.3 μM. Therefore, 0.3 μM propranolol was chosen as a concentration that would completely block β1 and β2 receptors (Ki = 1-5 nM) but would leave β3 receptors largely intact in the rat stomach fundus. In the presence of propranolol, several β-adrenergic receptor agonists relaxed the rat stomach fundus with a rank potency order of (R,R)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]-propyl]1,3-benzodioxole-2,2-dicarboxylate (CL316,243) > isoproterenol > norepinephrine = epinephrine = dL-4-3[[(1,1-dimethylethyl)amino]-2-hydroxylproproy]1,3 dihydro-2H-benzimidazol-2-one hydrochloride (CGP12177) > clenbuterol > terbutaline > pindolol. Isoproterenol, norepinephrine and epinephrine were full agonists, whereas (R,R)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]-amino]-propyl]1,3-benzodioxole-2,2-dicarboxylate was only a partial agonist with 66% intrinsic activity relative to isoproterenol. These same β agonists were also studied for their ability to stimulate adenylyl cyclase activity in Chinese hamster ovary cells expressing the cloned rat β3 receptor. For this series of β receptor agonists, the relaxant activity in the rat stomach fundus, as measured by potency (EC50) or intrinsic activity (maximal response), correlated well with the ability of these agonists to activate the recombinant rat β3 receptor. Thus the present studies provide mol.

and pharmacol. evidence that the "atypical" β receptor in the rat stomach fundus that mediates relaxation is the β3 receptor.

L4 ANSWER 156 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:11023 CAPLUS
DOCUMENT NUMBER: 123:132548
TITLE: Anti-obesity and anti-diabetic effects of CL 316,243, a highly specific β3-adrenoceptor agonist, in yellow KK mice. [Erratum to document cited in CA120:95410s]
AUTHOR(S): Yoshida, Toshihide; Sakane, Naoki; Wakabayashi, Yasuo; Umekawa, Tsunekazu; Kondo, Motoharu
CORPORATE SOURCE: First Dep. Int. Med., Kyoto Prefect. Univ. Med., Kyoto, 602, Japan
SOURCE: Life Sciences (1994), 54(22), 1745
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidiabetic and antiobesity action of, as β3-adrenergic agonist (Erratum))
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



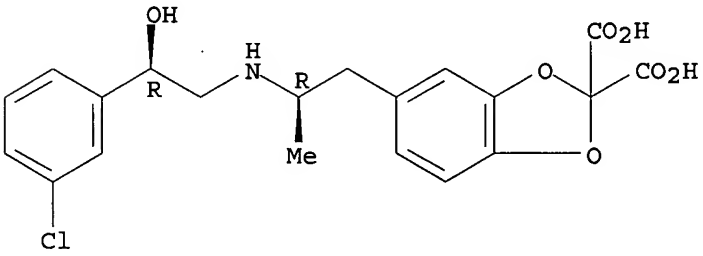
●2 Na

AB A corrected Figure 4 is given. The errors were not reflected in the abstract or
the index entries.

L4 ANSWER 157 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:645501 CAPLUS
DOCUMENT NUMBER: 121:245501
TITLE: Enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in the rat
AUTHOR(S): Kuratani, Kazuyoshi; Kodama, Hiroshi; Yamaguchi, Isamu
CORPORATE SOURCE: Tsukuba Res. Labs., Fujisawa Pharm. Co. Ltd., Tsukuba, 300-26, Japan
SOURCE: Journal of Pharmacology and Experimental Therapeutics

(1994), 270(2), 559-65
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhancement of gastric mucosal blood flow by beta-3 adrenergic agonists prevents indomethacin-induced antral ulcer in rat)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB Indomethacin (32 mg/kg s.c.) produced mainly antral ulcers in refed rats but almost exclusively corpus erosions in fasted rats. S.c. doses of a nonselective beta (isoproterenol), a selective β-2 (salbutamol) and selective β-3 adrenergic agonists BRL 35135, CL 316243, SR 58611A, dose-dependently attenuated the antral ulcers, and their activities were in the order of BRL 35135 (ED50 = 0.03 mg/kg) > CL 316243 (ED50 = 0.04 mg/kg) > SR 68511A (ED50 = 0.2 mg/kg) > isoproterenol (ED50 = 0.4 mg/kg) > salbutamol (ED50 = 6 mg/kg). Whereas only isoproterenol, salbutamol and BRL35135 significantly attenuated the corpus erosions and reduced gastric acid secretion in pylorus-ligated rats. In in vitro, all the beta agonists enhanced the beating rate of guinea pig atria (β-1 action) and inhibited spontaneous contractions of rat uterus (β-2 action) and colon (β-3 action). There was found a statistically significant correlation between the IC50 values of the drugs on the colon and ED50 values on the indomethacin-induced antral ulcers (r = 0.97). In addition, the beta agonists excepting salbutamol increased antral gastric mucosal blood flow in rats anesthetized with halothane, and the activities were arranged in the potency order of inhibiting colon motility. It is concluded that activation of β-3 adrenoceptor attenuates the indomethacin-induced antral ulcers through an enhancement of antral gastric mucosal blood flow, whereas activation of beta-1 and/or β-2 adrenoceptors attenuates indomethacin-induced corpus erosions through an inhibition of gastric secretion.

L4 ANSWER 158 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:621606 CAPLUS
DOCUMENT NUMBER: 121:221606
TITLE: Anti-obesity effect of CL 316,243, a highly specific

β3-adrenoceptor agonist, in mice with monosodium-L-glutamate-induced obesity

AUTHOR(S): Yoshida, Toshihide; Sakane, Naoki; Wakabayashi, Yasuo; Umekawa, Tsunekazu; Kondo, Motoharu

CORPORATE SOURCE: First Dept. of Internal Medicine, Kyoto Prefectural Univ. of Medicine, Kyoto, Japan

SOURCE: European Journal of Endocrinology (1994), 131(1), 97-102
CODEN: EJOEEP; ISSN: 0804-4643

DOCUMENT TYPE: Journal

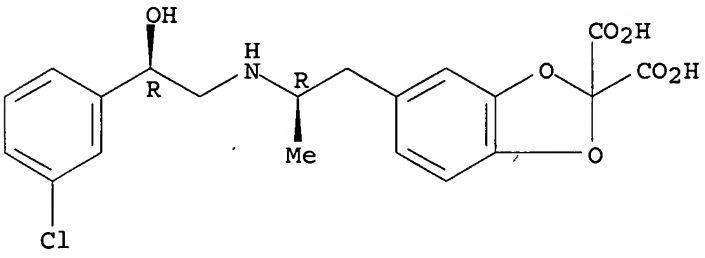
LANGUAGE: English

IT **138908-40-4**, CL 316243
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiobesity effect of CL 316,243)

RN 138908-40-4 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

AB The effects of CL 316,243, a high specific β3-adrenoceptor agonist (relative selectivities of 0, 1 and 100,000 for β1-, β2-, and β3-receptors, resp.), were evaluated in mice with monosodium L-glutamate (MSG)-induced obesity, as well as in control mice injected with physiol. saline instead of MSG. Both MSG- and saline-treated mice were divided into 3 groups and at 8 wk of age received either CL 316,243 (0.1 of 1.0 mg/kg) or distilled water through a gastric tube for 2 wk. CL 316,243 not only reduced white adipose tissue mass but also activated brown adipose tissue and systemic metabolism, and hence reduced body mass without affecting food intake. Furthermore, CL 316,243 decreased hyperglycemia and hypertriglyceridemia in MSG-treated mice. However, at the higher dose, CL 316,243 also increased liver triglyceride in MSG-treated mice. These observations suggest that CL 316,243 exerts an anti-obesity effect in mice with MSG-induced obesity and consequently may prove efficacious in the treatment of human obesity.

L4 ANSWER 159 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN

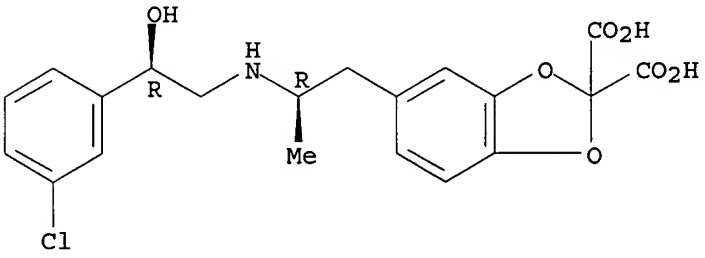
ACCESSION NUMBER: 1994:549595 CAPLUS

DOCUMENT NUMBER: 121:149595

TITLE: β-Adrenergic control of lipolysis in primate white fat cells: a comparative study with nonprimate mammals

AUTHOR(S): Bousquet-Melou, Alain; Galitzky, Jean; Carpene, Christian; Lafontan, Max; Berlan, Michel
CORPORATE SOURCE: Faculte de Medecine, Universite Paul Sabatier, Toulouse, 31073, Fr.
SOURCE: American Journal of Physiology (1994), 267(1, Pt. 2), R115-R123
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL-316243
RL: BIOL (Biological study)
(lipolysis stimulation by, in adipose tissue of human and mammals)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



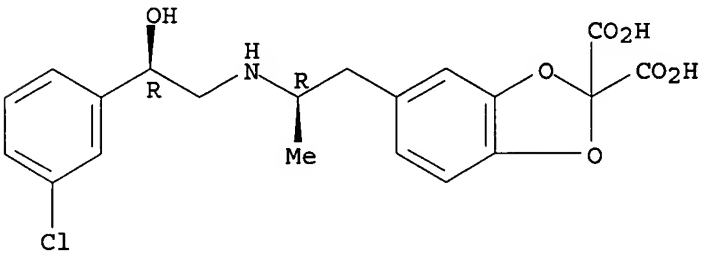
AB The β-adrenoceptor subtypes involved in the control of lipolysis in white fat cells of rat, dog, marmoset (Callithrix jacchus), baboon (Papio papio), macaque (Macaca fascicularis), and human were compared. In all species, [3H]CGP-12177 binding (up to 3 nM) indicated the existence of a homogeneous population of binding sites in fat cell membranes, and competition studies showed that β1- and β2-adrenoceptors were present. Selective β1- or β2-adrenoceptor agonists induced lipolysis. The efficiencies of isoproterenol and norepinephrine were similar. The use of selective β3-adrenoceptor agonists revealed that BRL-37344 and CL-316243 were full agonists, whereas CGP-12177 and SR-58611A were partial agonists in rat and dog white fat cells. β3-Agonists partially stimulated lipolysis in the marmoset, while CGP-12177 was weakly active in the baboon. In macaque and human fat cells, B3-agonists were ineffective. The lipolytic effect of norepinephrine involves β1-and/or β2-adrenoceptors in baboon, macaque, and human. The baboon and macaque constitute valuable models for studying the β-adrenergic control of lipolysis.

L4 ANSWER 160 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:473669 CAPLUS
DOCUMENT NUMBER: 121:73669
TITLE: Antidiabetic and antiobesity effects of a highly selective β3-adrenoceptor agonist (CL 316,243)
AUTHOR(S): Largis, Elwood E.; Burns, Michael G.; Muenkel, Helen A.; Dolan, Jo Alene; Claus, Thomas H.
CORPORATE SOURCE: American Cyanamid Co., Med. Res. Division, Pearl

River, NY, 10965, USA
SOURCE: Drug Development Research (1994), 32(2), 69-76
CODEN: DDREDK; ISSN: 0272-4391
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **138908-40-4**, CL 316243
RL: BIOL (Biological study)
(antidiabetic and antiobesity and thermogenic activities of, as β3-adrenergic receptor agonist)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

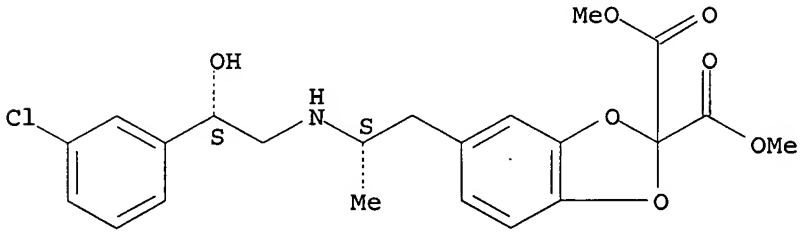
Absolute stereochemistry.



●2 Na

IT **138908-34-6**, CL 314698
RL: BIOL (Biological study)
(antidiabetic and antiobesity and thermogenic activities of, β3-adrenergic receptor agonist activity in relation to)
RN 138908-34-6 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

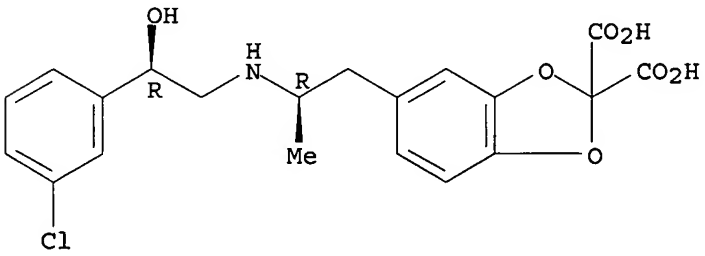


AB A third β-adrenoceptor subtype has been cloned from the rat, mouse, and human genomes. The presence of these receptors primarily on adipose tissue has raised the possibility that β3-adrenoceptor selective agonists may be useful antiobesity agents. CL 316,243 is a highly selective β3-agonist; it has a >30,000 to 1 β3-to-β1-adrenoceptor selectivity ratio and a 10,000 to 1 β3-to-β2-adrenoceptor selectivity ratio in in vitro functional assays. In vivo, animals were treated with CL 314,698, a diester prodrug of CL 316,243,

which is rapidly converted to CL 316,243. In obese (ob/ob) and diabetic (db/db) mice, treatment with Cl 314,698 reduced their hyperglycemia to the euglycemia of their lean littermates, and decreased plasma insulin levels. In obese mice, the compound also caused decreased weight gain despite increased food consumption, and the decreased weight was due to loss of fat while lean body mass was spared. CL 314,698 treatment also improved both glucose and insulin tolerance in obese mice, suggesting that it decreased insulin resistance. CL 314,698 also prevented further weight gain, without affecting food consumption, in rats previously made obese by feeding a high fat diet. The compound reduced plasma insulin and triglyceride levels, and reduced fat pad wts., while having no effect on plasma glucose, cholesterol, thyroxine, or T3 levels or on skeletal muscle weight Decreased weight gain without decreased food consumption suggested that CL 316,243 stimulated thermogenesis. Treatment of obese mice for 3 wk with CL 316,243 increased thermogenesis by 45% as measured by indirect calorimetry. Thus, CL 316,243 is a potent, β3-adrenoceptor selective agonist with thermogenic, antidiabetic, and antiobesity properties in several models of non-insulin dependent diabetes and obesity.

L4 ANSWER 161 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:473519 CAPLUS
DOCUMENT NUMBER: 121:73519
TITLE: Beta-3 adrenoceptor selectivity of the dioxolane dicarboxylate phenethanolamines
AUTHOR(S): Dolan, Jo Alene; Muenkel, Helen A.; Burns, Michael G.; Pellegrino, Susan M.; Fraser, Claire M.; Pietri, France; Strosberg, A. Donny; Largis, Elwood E.; Dutia, Minu D.; et al.
CORPORATE SOURCE: Cardiovascular Mol. Biol. Dep., American Cyanamid Co., Pearl River, NY, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 269(3), 1000-6
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243 **139014-45-2**, CL 314514
RL: BIOL (Biological study)
(β adrenergic properties of, in various tissues, treatment of diabetes and obesity in relation to)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

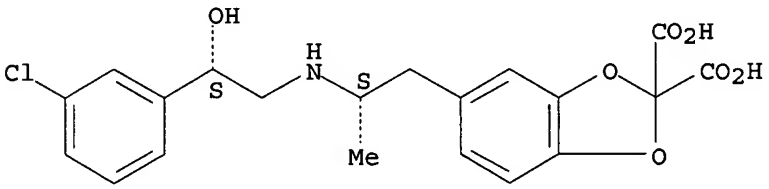
Absolute stereochemistry.



●2 Na

RN 139014-45-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



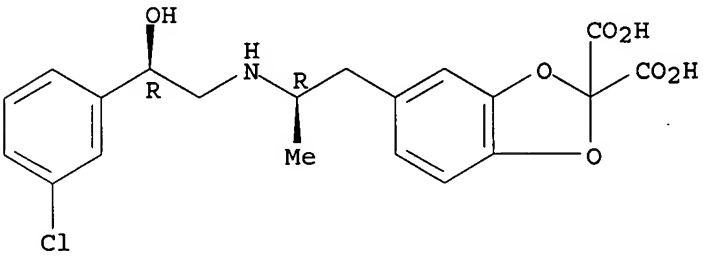
●2 Na

AB The beta-1, beta-2 and beta-3 adrenergic properties of several benzodioxole-containing phenethranolamines were determined in vitro in both functional and binding assays. In addition, two of the compds. were evaluated for their effects on radioligand binding and cAMP production in stably transfected Chinese Hamster Ovary (CHO) cells expressing the cloned rat or human beta-3 adrenoceptor or the human beta-2 or beta-1 adrenoceptor. The (±)-R*,R*-racemate, CL 314,514, and the pure (-)-R,R enantiomer, CL 316,243, stimulated rat adipocyte lipolysis (beta-3 effect) with EC50 values in the low nanomolar range, while having no effect on the rate of contraction of guinea pig atria (beta-1 effect) and little or no ability to prevent the insulin-stimulated incorporation of [14C]glucose into rat soleus muscle glycogen (beta-2 effect) with concns. as great as 100 μM. The lack of beta-1 and beta-2 adrenergic activity was confirmed by the low affinity of compds. for beta-1 or beta-2 adrenoceptors in plasma membranes from rat heart or rat soleus muscle, resp. In CHO cells expressing each human beta adrenoceptor subtype, CL 314,514 bound to beta-3-CHO cells with a Ki of 2 μM and stimulated cAMP production with an activation constant (Kact) of 1 μM, whereas it did not bind to either beta-1- or beta-2-CHO cells at 100 μM. CL 316,243 bound to membranes from rat beta-3-CHO cells with a Ki of 1 μM and stimulated cAMP production in beta-3-CHO cells with a Kact of 0.7 nM. These results indicate that CL 314,514 and CL 316,243 are highly selective agonists for the beta-3 adrenoceptor and as such may be useful for the treatment of diabetes and obesity.

L4 ANSWER 162 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:315571 CAPLUS
DOCUMENT NUMBER: 120:315571
TITLE: Effect of CL-316,243, a thermogenic β3-agonist, on energy balance and brown and white adipose tissues in rats
AUTHOR(S): Himms-Hagen, Jean; Cui, Jingying; Danforth, Elliot, Jr.; Taatjes, Douglas J.; Lang, Susan S.; Waters, Brenda L.; Claus, Thomas H.
CORPORATE SOURCE: Dep. Biochem., Univ. Ottawa, Ottawa, ON, K1H 8M5, Can.
SOURCE: American Journal of Physiology (1994), 266(4, Pt. 2), R1371-R1382
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal

LANGUAGE: English
IT **138908-40-4**, CL-316243
RL: BIOL (Biological study)
(adipose tissue and energy balance response to, as thermogen, obesity treatment in relation to)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



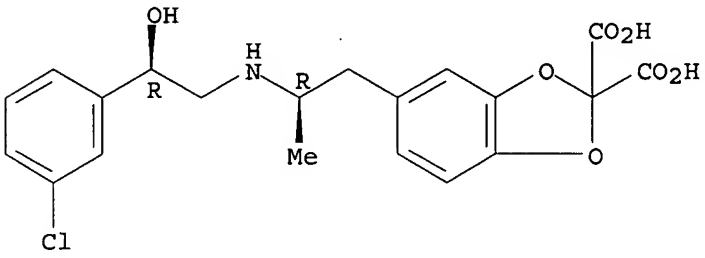
●2 Na

AB The objective was to assess the effect of a new, highly selective, β3-adrenergic agonist, CL-316,243 (CL), on energy balance and brown and white adipose tissue (BAT and WAT, resp.) in young rats eating a high-fat diet to induce obesity. Chronic treatment with CL increased body temperature and 24-h energy expenditure, mainly by increasing resting metabolic rate. Food intake was not altered but carcass fat was reduced. Interscapular BAT was markedly hypertrophied, with three- or fourfold increases in the content of uncoupling protein (UCP) and cytochrome oxidase. Quant. immunoelectron microscopy of interscapular BAT of CL-treated rats showed smaller mitochondria with an unchanged total amount of UCP per mitochondrion. The relative frequency of the four major cell types in BAT (mature brown adipocytes, preadipocytes, interstitial cells, endothelial cells) was not altered. The CL-induced hypertrophy differed from that induced by chronic stimulation by endogenous norepinephrine (as in cold-adaptation) in absence of hyperplasia (there was a slightly reduced DNA content), absence of an increase in the thyroxine (T4) 5'-deiodinase activity, and absence of a selective increase in UCP concentration
WAT depots weighed less and had fewer cells (lower DNA content) in the CL-treated rats. Some multilocular adipocytes appeared in these normally almost exclusively unilocular WAT depots (mesenteric, inguinal, epididymal, retroperitoneal). The authors conclude that CL not only promotes BAT mitochondrial proliferation and thermogenesis and overall energy expenditure and leanness, but also retards the development of WAT hyperplasia during the early stage of diet-induced obesity.

L4 ANSWER 163 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:95410 CAPLUS
DOCUMENT NUMBER: 120:95410
TITLE: Anti-obesity and anti-diabetic effects of CL 316,243, a highly specific β3-adrenoceptor agonist, in yellow KK mice
AUTHOR(S): Yoshida, Toshihide; Sakane, Naoki; Wakabayashi, Yasuo;

Umekawa, Tsunekazu; Kondo, Motoharu
CORPORATE SOURCE: First Dep. Int. Med., Kyoto Prefect. Univ. Med., Kyoto, 602, Japan
SOURCE: Life Sciences (1994), 54(7), 491-8
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **138908-40-4**, CL 316243
RL: PROC (Process)
(antidiabetic and antiobesity action of, as β3-adrenergic agonist)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.

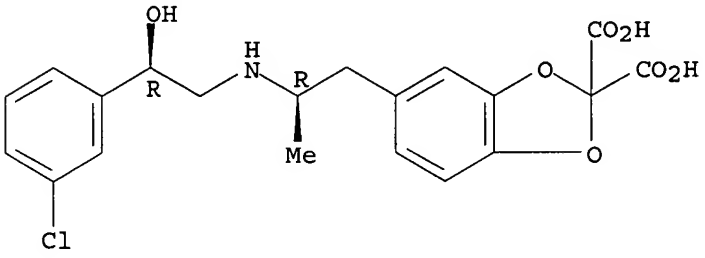


AB The anti-obesity and anti-diabetic effects of CL 316,243, a highly specific β3-adrenoceptor agonist (β1:β2:β3 = 0:1:100,000), were evaluated in obese diabetic yellow KK mice and C57Bl control mice. The compound was fed through a gastric tube at a rate of 0.1 mg/kg/day for 2 wk. The following parameters were compared in the treated and control animals given distilled water: brown adipose tissue thermogenesis, resting metabolic rate, insulin receptors in adipocytes, and blood glucose and serum insulin levels during a glucose overloading test. CL 316,243 significantly increased brown adipose tissue thermogenesis and resting metabolic rate in both yellow KK mice and C57B1 controls. The amount of white adipose tissue decreased, although food intake was not affected. The effects contributed to the mitigation of obesity in yellow KK mice. CL 316,243 also increased the concentration of insulin receptors and decreased the levels of serum insulin and blood glucose during the glucose overloading test in yellow KK mice. These observations suggest that CL 316,243 possesses anti-obesity and anti-diabetic effects and consequently may be useful for treating obesity as well as non-insulin-dependent diabetes mellitus in obese persons, without causing excessive side effects.

L4 ANSWER 164 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:641324 CAPLUS
DOCUMENT NUMBER: 119:241324
TITLE: Antiobesity action of highly β3-selective adrenoceptor agonist, CL 316, 243
AUTHOR(S): Yoshida, Toshihide; Sakane, Naoki; Umekawa, Tsunekazu; Wakabayashi, Yasuo; Kondo, Motoharu
CORPORATE SOURCE: Kyoto Prefect. Univ. Med., Kyoto, 602, Japan

SOURCE: Igaku no Ayumi (1993), 166(2), 145-6
CODEN: IGAYAY; ISSN: 0039-2359
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
IT **138908-40-4**, CL 316243
RL: BIOL (Biological study)
(antiobesity activity of, brown adipose tissue GDP-binding ability in relation to)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



AB CL316,243 was administered at 0.1 or 1.0 mg/kg p.o. to mice with mono-Na glutamate-induced obesity to show less body weight, less retroperitoneal white adipose tissue weight, higher resting metabolic rate, and higher brown adipose tissue GDP-binding ability than nontreated obesity mice.

L4 ANSWER 165 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:571420 CAPLUS
DOCUMENT NUMBER: 117:171420
TITLE: [[(2-Hydroxy-2-phenyl)ethyl]amino]alkyl]-1,3-benzodioxoles, methods for their preparation and their use for increasing lean meat in edible animals and as antidiabetic and antiobesity agents
INVENTOR(S): Bloom, Jonathan D.; Claus, Thomas H.; DeVries, Vern G.; Dolan, Jo A.; Dutia, Minu D.
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: U.S., 23 pp. Cont.-in-part of U.S. Ser. No. 519,192.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5106867	A	19920421	US 1991-679313	19910405
US 5061727	A	19911029	US 1990-519192	19900504
PRIORITY APPLN. INFO.:			US 1990-519192 A2	19900504

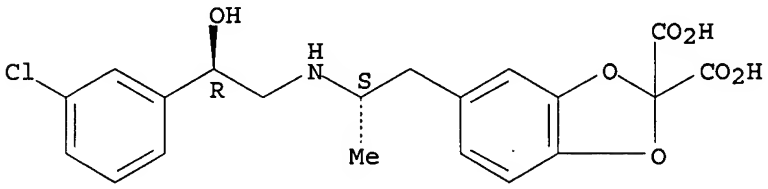
OTHER SOURCE(S): CASREACT 117:171420; MARPAT 117:171420
IT **139013-10-8 143485-17-0 143485-18-1**
RL: RCT (Reactant); RACT (Reactant or reagent)

(antiobesity agent, antidiabetic, and animal food additive)

RN 139013-10-8 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

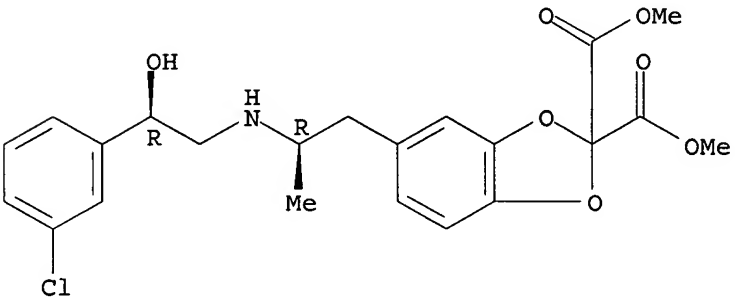


●2 Na

RN 143485-17-0 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, hydrobromide, [R-(R*,R*)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

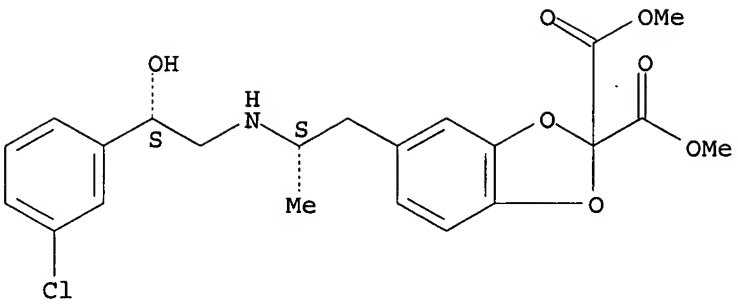


● HBr

RN 143485-18-1 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, hydrobromide, [S-(R*,R*)]-(9CI) (CA INDEX NAME)

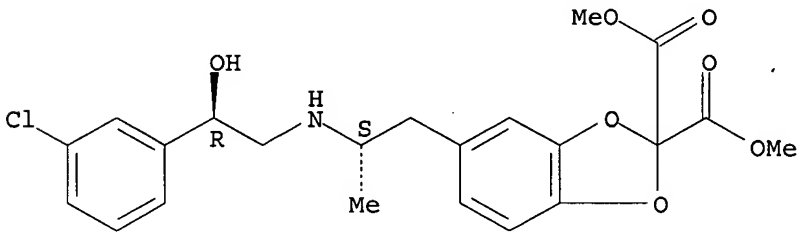
Absolute stereochemistry.



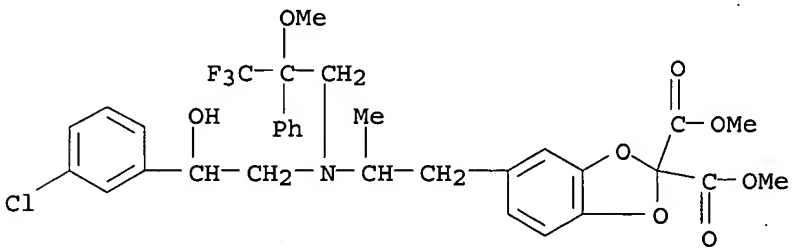
● HBr

IT **138908-44-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and alkylation of, with bromoacetate)
RN 138908-44-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

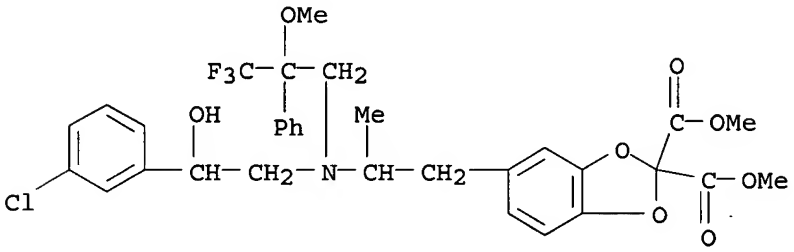
Relative stereochemistry.



IT **143485-14-7P 143563-34-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of)
RN 143485-14-7 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl](3,3,3-trifluoro-2-methoxy-2-phenylpropyl)amino]propyl]-, dimethyl ester, stereoisomer (9CI) (CA INDEX NAME)

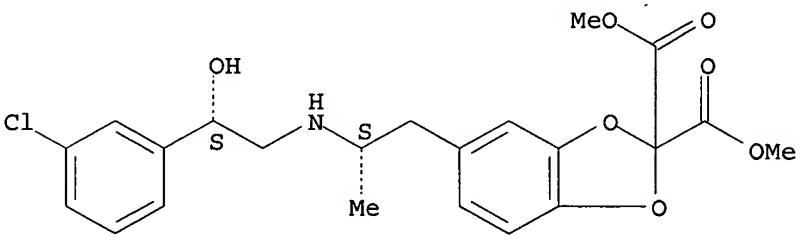


RN 143563-34-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl](3,3,3-trifluoro-2-methoxy-2-phenylpropyl)amino]propyl]-, dimethyl ester, stereoisomer (9CI) (CA INDEX NAME)



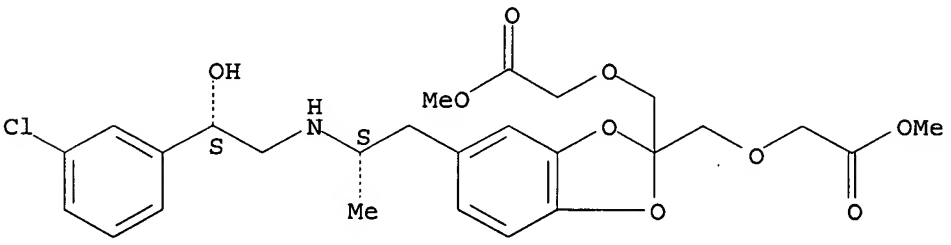
IT **138908-34-6P 138908-35-7P 138908-36-8P**
138908-40-4P 138908-41-5P 138908-54-0P
138908-59-5P 138908-60-8P 139014-45-2P
143485-19-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antiobesity agent, antidiabetic, and animal food additive)
RN 138908-34-6 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 138908-35-7 CAPLUS
CN Acetic acid, 2,2'-[[5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxol-2-ylidene]bis(methyleneoxy)]bis-, dimethyl ester, (R*,R*)-(9CI) (CA INDEX NAME)

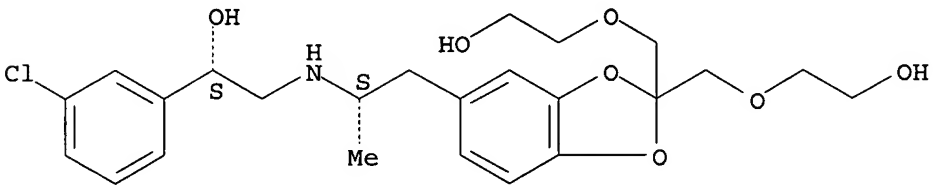
Relative stereochemistry.



RN 138908-36-8 CAPLUS

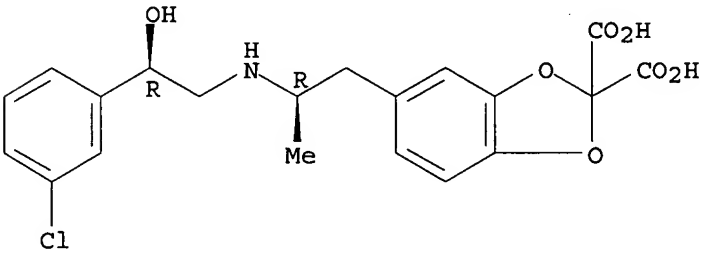
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

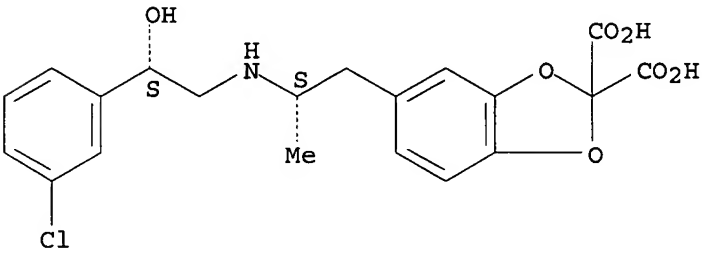
Absolute stereochemistry.



●2 Na

RN 138908-41-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

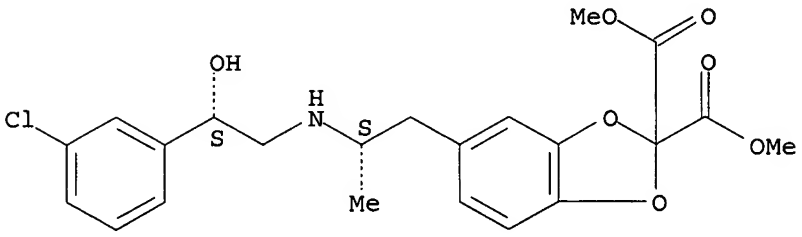


●2 Na

RN 138908-54-0 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, hydrobromide, (R*,R*)- (9CI) (CA INDEX NAME)

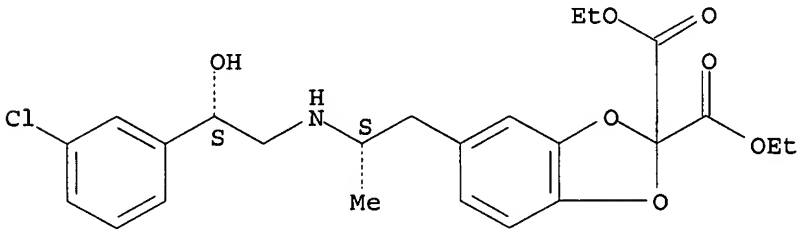
Relative stereochemistry.



● HBr

RN 138908-59-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, hydrobromide, (R*,R*)- (9CI) (CA INDEX NAME)

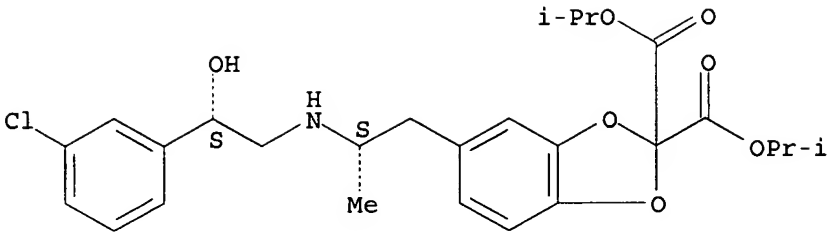
Relative stereochemistry.



● HBr

RN 138908-60-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, hydrobromide, (R*,R*)- (9CI) (CA INDEX NAME)

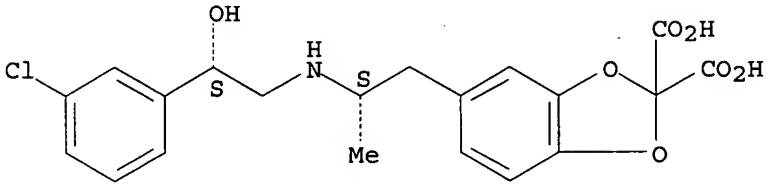
Relative stereochemistry.



● HBr

RN 139014-45-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, rel- (9CI) (CA INDEX NAME)

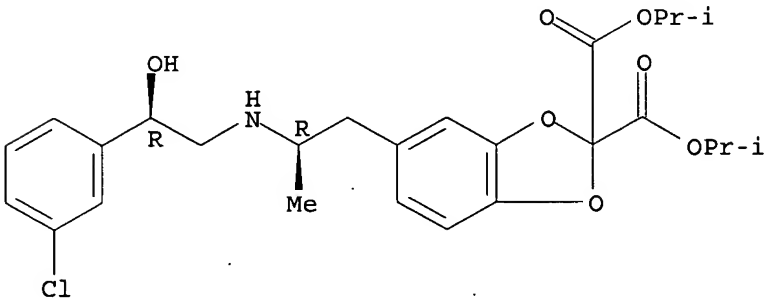
Relative stereochemistry.



●2 Na

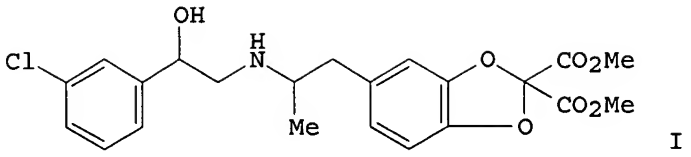
RN 143485-19-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

GI

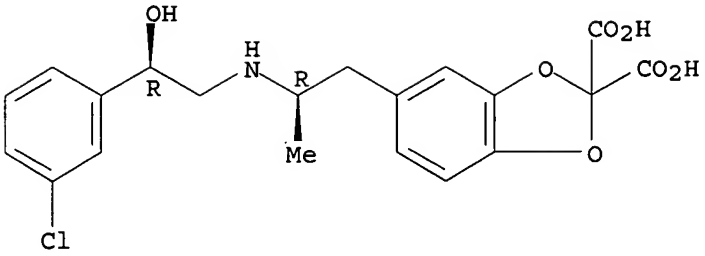


I

AB A method for increasing the lean meat content in edible animals comprises the administration of certain 5-[[(2-hydroxy-2-phenyl)ethyl]amino]alkyl]-1,3-benzodioxole derivs. Some benzodioxole derivs., e.g. di-Me (R*,R*)-5-[2-[2-(3-chlorophenyl)-2-hydroxyethyl)amino]-1-methylethyl]-1,3-benzodioxole-2,2-dicarboxylate (I), are claimed. I-HBr was prepared in several steps. I-HBr (200 ppm in diet) had an antilipogenic effect in mice; i.e. the fat-to-body weight ratio was 1:43, whereas it was 1:13 in an untreated control. I lowered blood glucose levels in hypoglycemic mice.

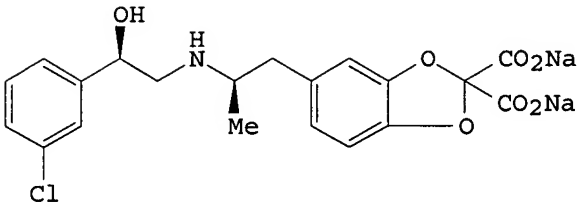
L4 ANSWER 166 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:531102 CAPLUS
DOCUMENT NUMBER: 117:131102
TITLE: Disodium (R,R)-5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxole-2,2-dicarboxylate (CL 316,243). A potent β-adrenergic agonist virtually specific for β3 receptors. A promising antidiabetic and antiobesity agent
AUTHOR(S): Bloom, Jonathan D.; Dutia, Minu D.; Johnson, Bernard D.; Wissner, Allan; Burns, Michael G.; Largis, Elwood E.; Dolan, Jo Alene; Claus, Thomas H.
CORPORATE SOURCE: Lederle Lab., Am. Cyanamid Co., Pearl River, NY, 10965, USA
SOURCE: Journal of Medicinal Chemistry (1992), 35(16), 3081-4
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 117:131102
IT **138908-40-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and β-adrenergic agonist, antidiabetic and antiobesity activity of)
RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

Absolute stereochemistry.



●2 Na

GI



I

AB The chiral synthesis and biol. evaluation of the title compound, CL 316,243 (I) is described. I was prepared as the single active (R,R) enantiomer by a multistep synthesis involving the condensation of a chiral amine with a chiral epoxide. Biol. evaluation included the ability of the compound to promote lipolysis in rat adipocytes (a β3 effect), as well as to stimulate guinea pig atrial rate of contraction (β1 effect) and to inhibit glycogen synthesis in rat soleus muscle (β2 effect). I was a potent and highly selective agonist for the β3 adrenergic receptor as well as a potent antihyperglycemic and antiobesity agent in genetically obese mice. The compound is currently in Phase I clin. trials.

L4 ANSWER 167 OF 167 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:106271 CAPLUS
DOCUMENT NUMBER: 116:106271
TITLE: Preparation of 5-[2-[(2-aryl-2-hydroxyethyl)amino]propyl]-1,3-benzodioxoles as hypoglycemic and antiobesity agents
INVENTOR(S): Bloom, Jonathan D.; Claus, Thomas H.; DeVries, Vern G.; Dolan, Jo A.; Dutia, Minu D.
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: U.S., 24 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

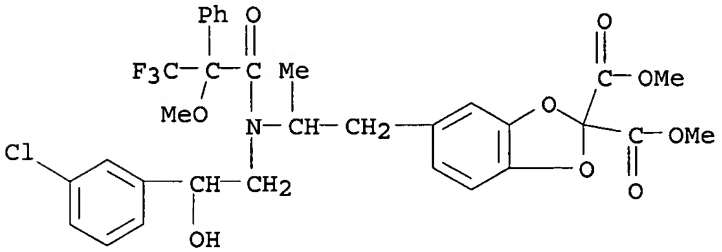
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 5061727	A	19911029	US 1990-519192	19900504
US 5106867	A	19920421	US 1991-679313	19910405
EP 455006	A2	19911106	EP 1991-105510	19910408
EP 455006	A3	19920401		
EP 455006	B1	19990707		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE				
AT 181914	E	19990715	AT 1991-105510	19910408
ES 2133273	T3	19990916	ES 1991-105510	19910408
IL 97900	A1	19970415	IL 1991-97900	19910419
AU 9176078	A1	19911107	AU 1991-76078	19910429
AU 639094	B2	19930715		
CA 2041712	AA	19911105	CA 1991-2041712	19910502
JP 05320153	A2	19931203	JP 1991-130413	19910502
PL 165665	B1	19950131	PL 1991-290119	19910502
FI 9102142	A	19911105	FI 1991-2142	19910503
FI 94862	B	19950731		
FI 94862	C	19951110		
NO 9101751	A	19911105	NO 1991-1751	19910503
NO 177822	B	19950821		
NO 177822	C	19951129		
ZA 9103366	A	19920325	ZA 1991-3366	19910503
HU 59918	A2	19920728	HU 1991-1495	19910503
HU 210596	B	19950529		
CZ 283420	B6	19980415	CZ 1991-1285	19910503
CN 1056495	A	19911127	CN 1991-102965	19910504
CN 1037348	B	19980211		
US 5151439	A	19920929	US 1991-742409	19910801
US 5245053	A	19930914	US 1992-896319	19920610
US 5373020	A	19941213	US 1993-71443	19930603
PRIORITY APPLN. INFO.:			US 1990-519192	A2 19900504
			US 1991-742409	A3 19910808
			US 1992-896319	A3 19920610

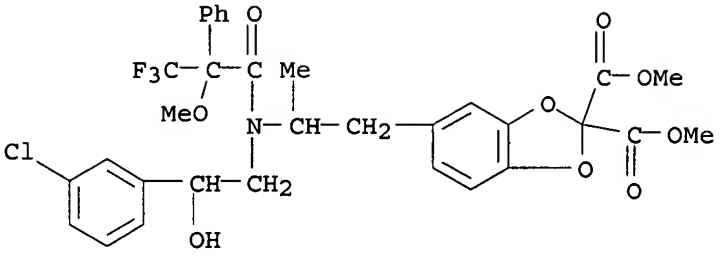
OTHER SOURCE(S): MARPAT 116:106271

IT **138908-55-1P 139013-11-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, in preparation of hypoglycemic and antiobesity agents)

RN 138908-55-1 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl](3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl)amino]propyl]-, dimethyl ester, stereoisomer (9CI) (CA INDEX NAME)



RN 139013-11-9 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl](3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl)amino]propyl]-, dimethyl ester, stereoisomer (9CI) (CA INDEX NAME)

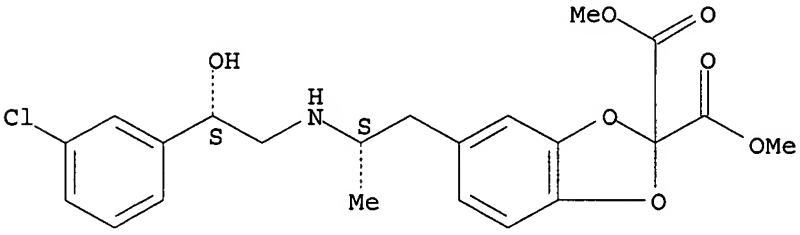


IT **138908-34-6P 138908-35-7P 138908-36-8P**
138908-38-0P 138908-39-1P 138908-40-4P
138908-41-5P 138908-42-6P 138908-43-7P
138908-44-8P 138908-45-9P 138908-46-0P
138908-54-0P 138908-59-5P 138908-60-8P
139012-91-2P 139012-92-3P 139012-93-4P
139012-94-5P 139012-95-6P 139012-96-7P
139012-97-8P 139012-98-9P 139012-99-0P
139013-00-6P 139013-01-7P 139013-02-8P
139013-03-9P 139013-04-0P 139013-05-1P
139013-06-2P 139013-07-3P 139013-08-4P
139013-09-5P 139013-10-8P 139014-45-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as hypoglycemic and antiobesity agent)

RN 138908-34-6 CAPLUS

CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, rel- (9CI) (CA INDEX NAME)

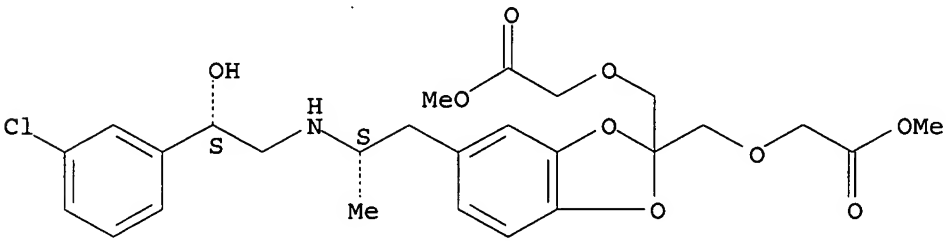
Relative stereochemistry.



RN 138908-35-7 CAPLUS

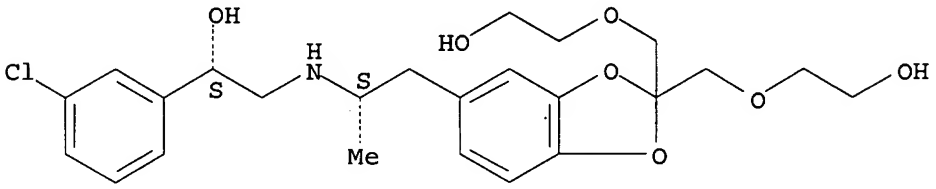
CN Acetic acid, 2,2'-[[5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxol-2-ylidene]bis(methyleneoxy)]bis-, dimethyl ester, (R*,R*)-(9CI) (CA INDEX NAME)

Relative stereochemistry.



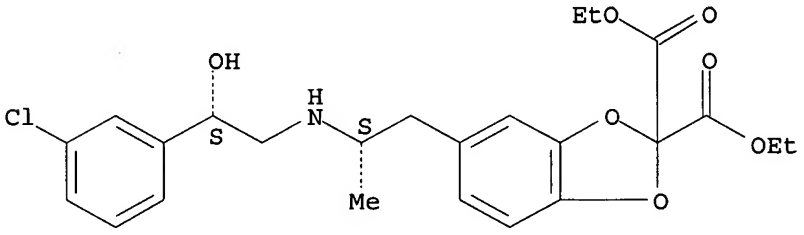
RN 138908-36-8 CAPLUS
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



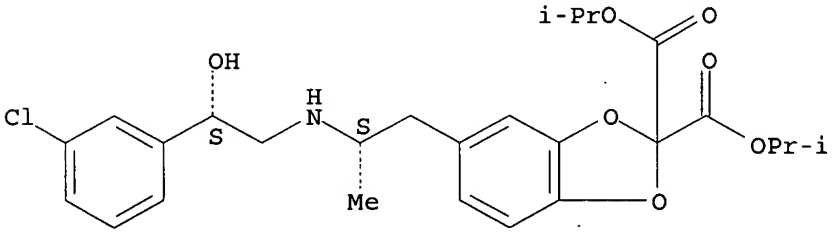
RN 138908-38-0 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



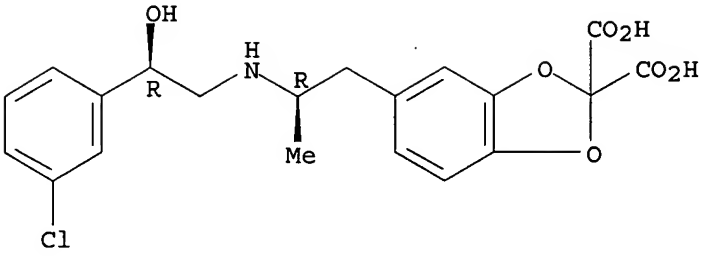
RN 138908-39-1 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 138908-40-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt (9CI) (CA INDEX NAME)

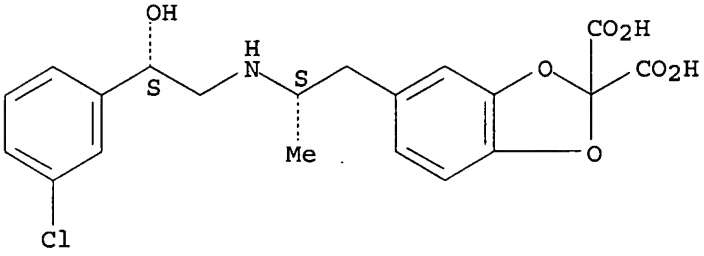
Absolute stereochemistry.



●2 Na

RN 138908-41-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

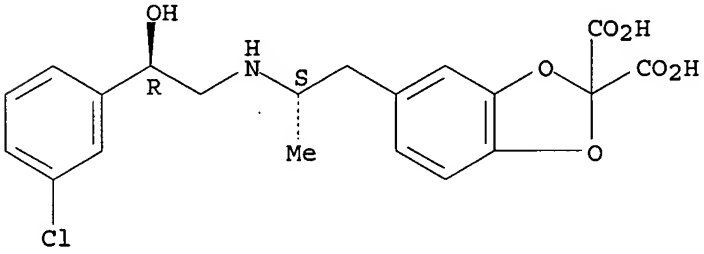
Absolute stereochemistry.



●2 Na

RN 138908-42-6 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

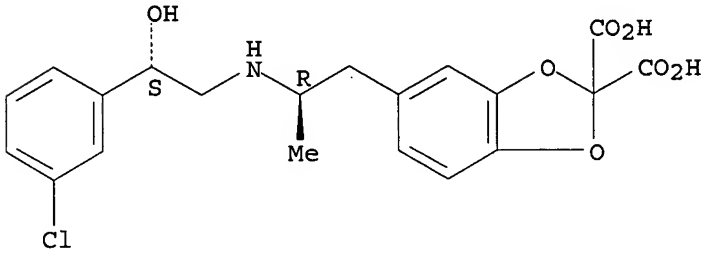
Absolute stereochemistry.



●2 Na

RN 138908-43-7 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

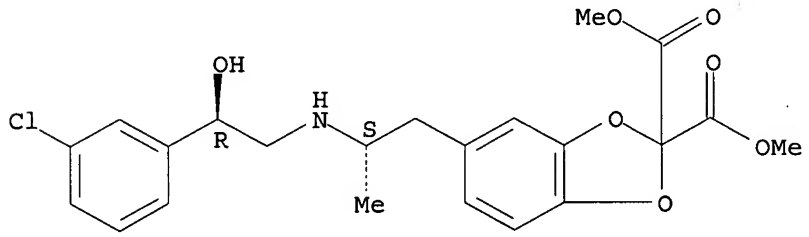
Absolute stereochemistry.



●2 Na

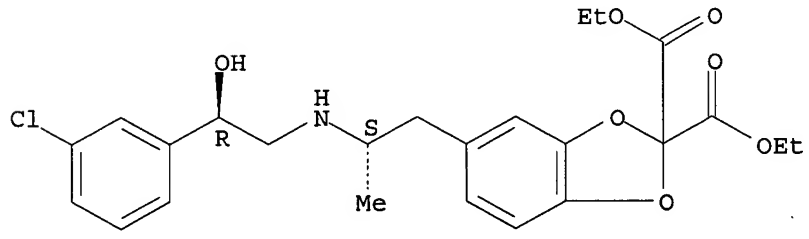
RN 138908-44-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



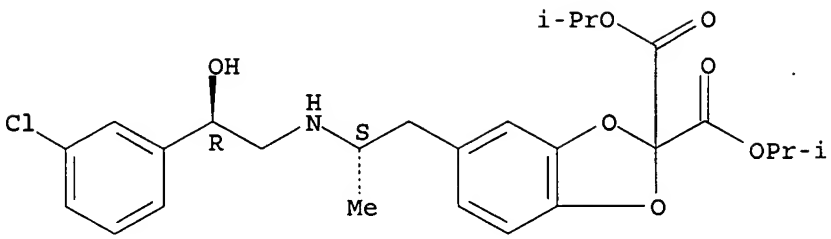
RN 138908-45-9 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



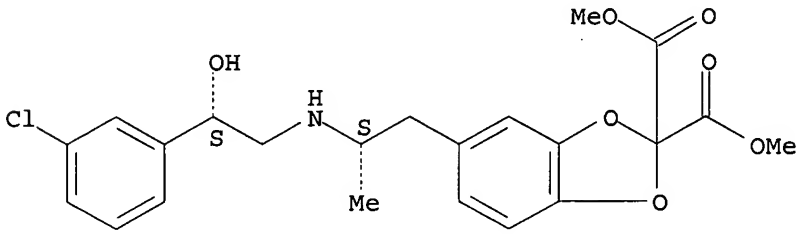
RN 138908-46-0 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, (R*,S*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 138908-54-0 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, hydrobromide, (R*,R*)- (9CI) (CA INDEX NAME)

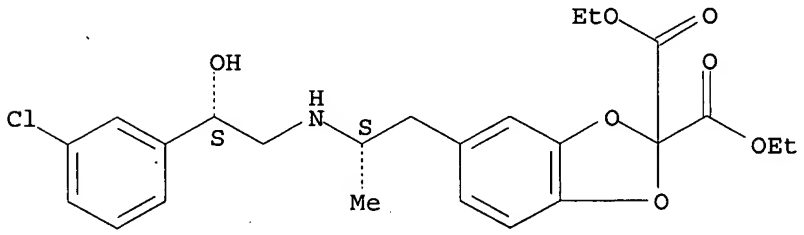
Relative stereochemistry.



● HBr

RN 138908-59-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, hydrobromide, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

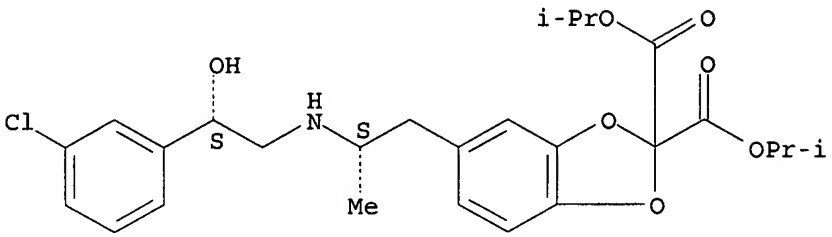


● HBr

RN 138908-60-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, hydrobromide,

(R*,R*)- (9CI) (CA INDEX NAME)

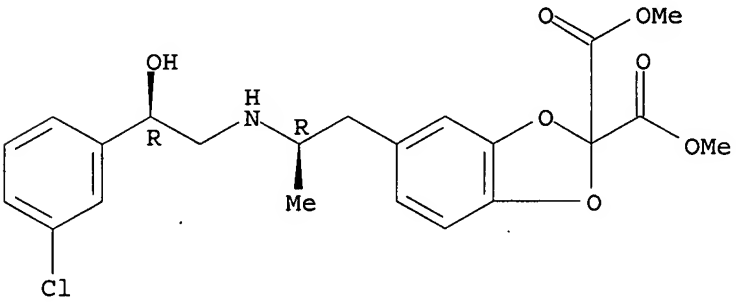
Relative stereochemistry.



● HBr

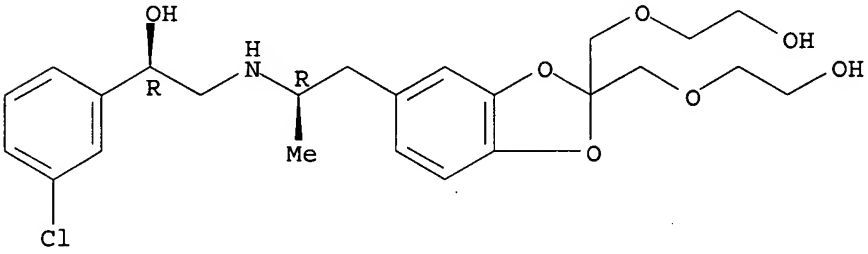
RN 139012-91-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139012-92-3 CAPLUS
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

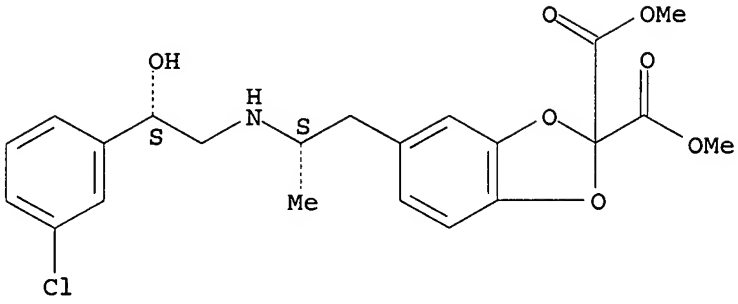
Absolute stereochemistry.



RN 139012-93-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX

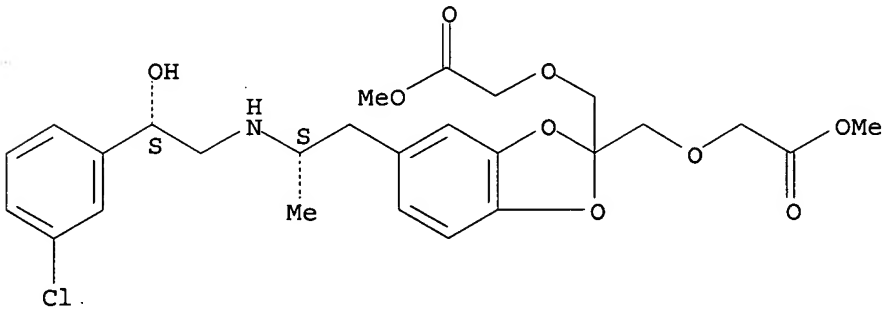
NAME)

Absolute stereochemistry.



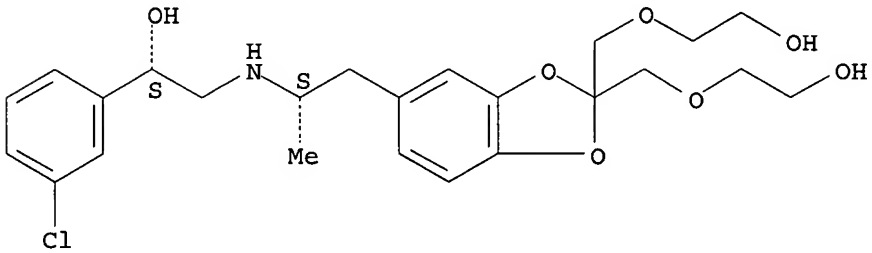
RN 139012-94-5 CAPLUS
CN Acetic acid, 2,2'-[[5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxol-2-ylidene]bis(methyleneoxy)]bis-, dimethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



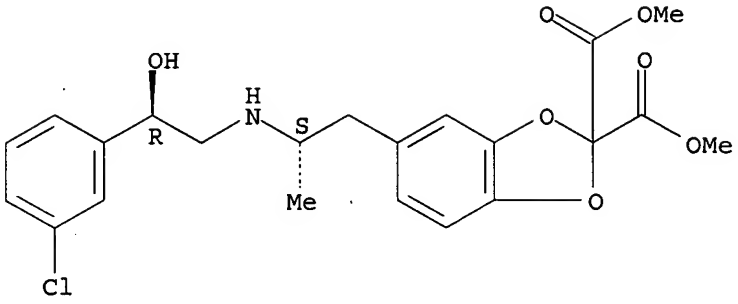
RN 139012-95-6 CAPLUS
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



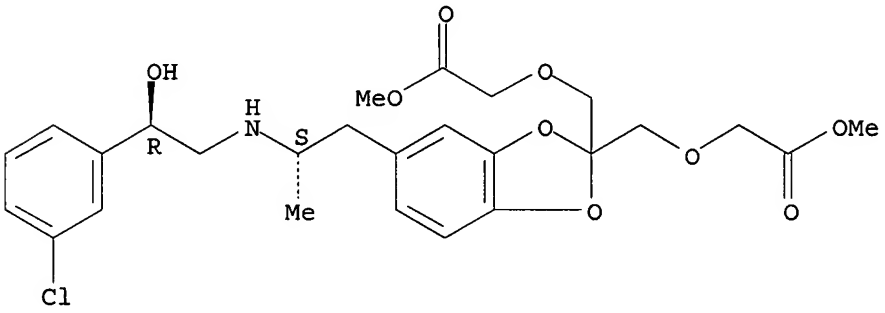
RN 139012-96-7 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



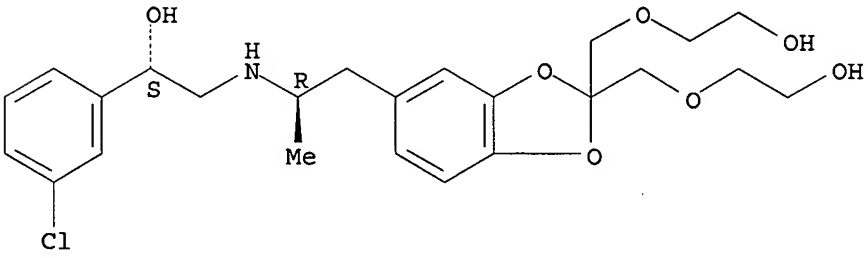
RN 139012-97-8 CAPLUS
CN Acetic acid, 2,2'-[[5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxol-2-ylidene]bis(methyleneoxy)]bis-, dimethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



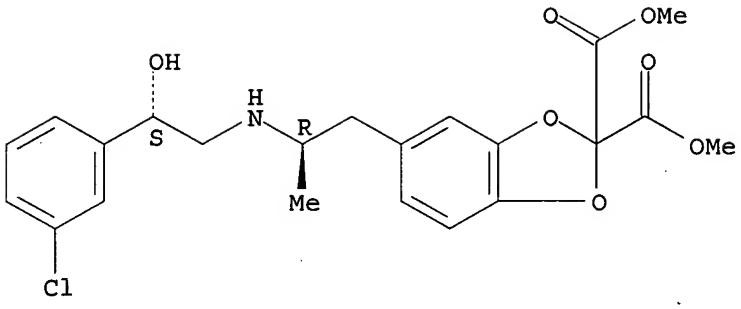
RN 139012-98-9 CAPLUS
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



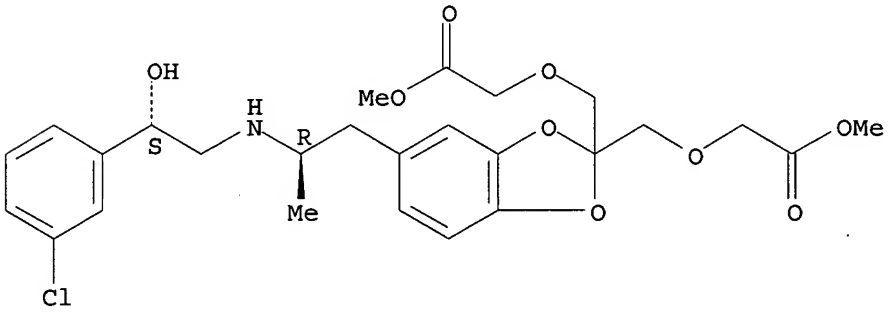
RN 139012-99-0 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, dimethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



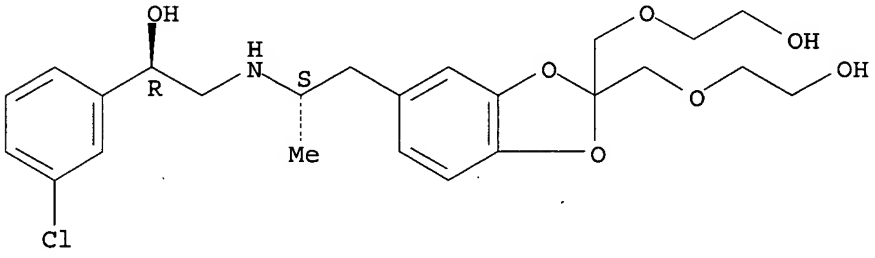
RN 139013-00-6 CAPLUS
CN Acetic acid, 2,2'-[[5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1,3-benzodioxol-2-ylidene]bis(methyleneoxy)]bis-, dimethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



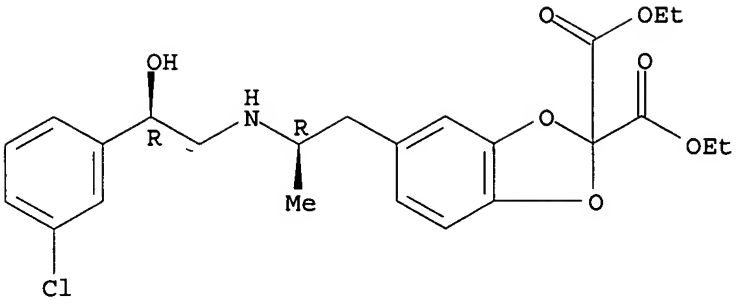
RN 139013-01-7 CAPLUS
CN Benzenemethanol, α-[[[2-[2,2-bis[(2-hydroxyethoxy)methyl]-1,3-benzodioxol-5-yl]-1-methylethyl]amino]methyl]-3-chloro-, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



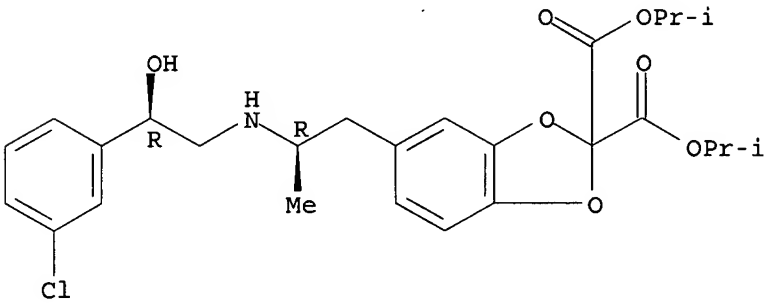
RN 139013-02-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



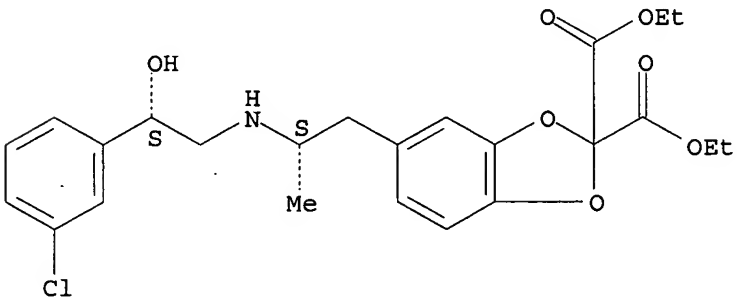
RN 139013-03-9 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



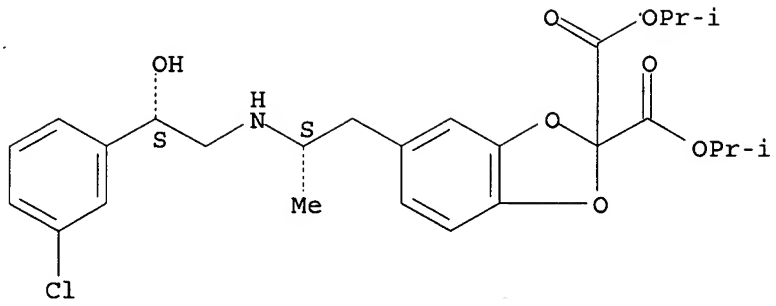
RN 139013-04-0 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



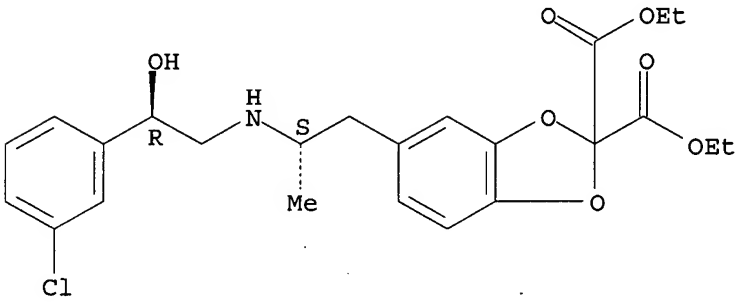
RN 139013-05-1 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



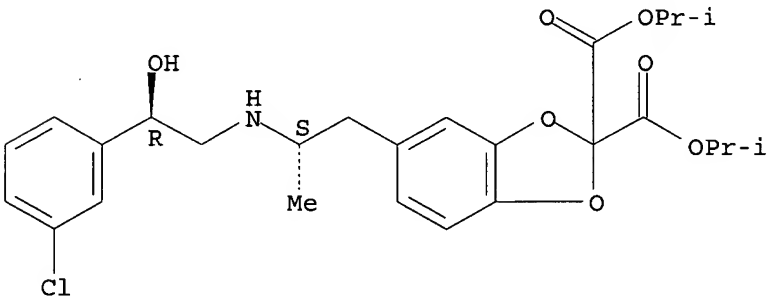
RN 139013-06-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



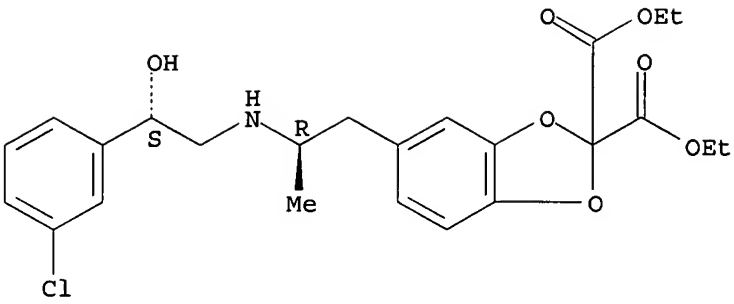
RN 139013-07-3 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, [R-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



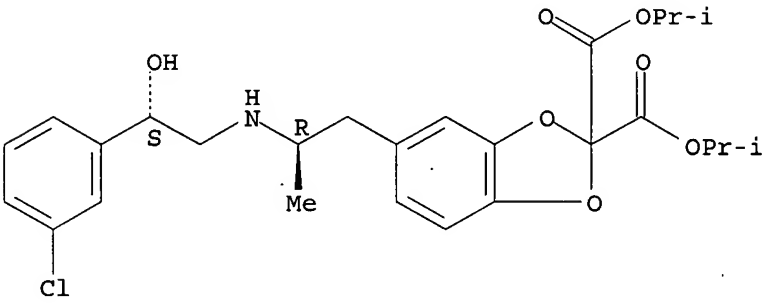
RN 139013-08-4 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, diethyl ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



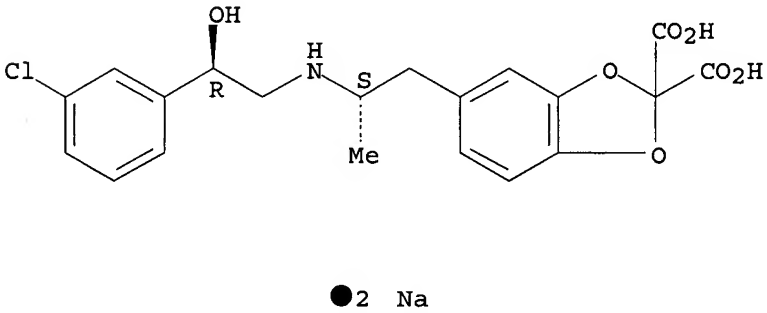
RN 139013-09-5 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, bis(1-methylethyl) ester, [S-(R*,S*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 139013-10-8 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[2-[[2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, (R*,S*)- (9CI) (CA INDEX NAME)

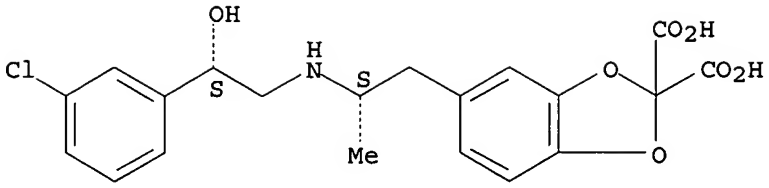
Relative stereochemistry.



●2 Na

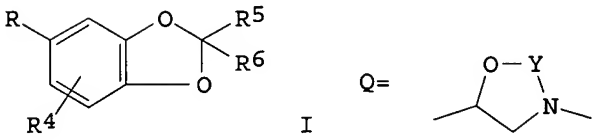
RN 139014-45-2 CAPLUS
CN 1,3-Benzodioxole-2,2-dicarboxylic acid, 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-, disodium salt, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

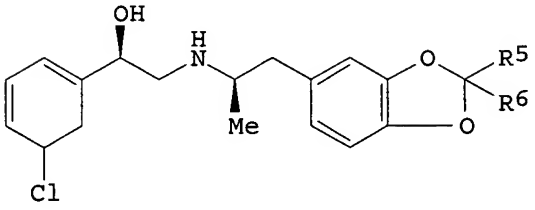


●2 Na

GI



I



III

AB Title compds. [I; R = R8XCR2R3CH2; R2, R3 = H, alkyl; R4 = H, alkyl, alkoxy, halo, OH, CF3, etc.; R5, R6 = H, CO2H, CH2OH, alkoxycarbonyl, etc.; R8 = (un)substituted Ph; X = CH(OR')CH2NR', oxazolediyl group Q; R' = H, alkyl, acyl; Y = CO, CS] were prepared Thus, 3,4-(MeO)2C6H3CH2COMe was reductively aminated by 3-ClC6H4CH(OH)NH2 (preparation given) and the product cyclized to give, after O-demethylation, (R*,S*)-(±)-3-ClC6H4QCHMeCH2C6H3(OH)2-3,4 (Y = CO) which was cyclocondensed with Br2C(CO2Et)2 to give (R*,S*)-(±)-I (R as above, R2 = Me, R3 = R4 = H, R8 = 3-ClC6H4, X = Q, Y = CO) (II; R5 = R6 = CO2Et). The latter was reduced and the product etherified by BrCH2CO2Me to give II (R5 = R6 = CH2OCH2CO2Me) which was hydrolized to give, after salification and reesterification, title compound (±)-III.HBr (IV). At 0.0005 weight% in feed IV gave reduction of plasma glucose levels in diabetic mice from 566 to 170 mg/dL after 7 wk.

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	828.16	990.56
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-119.72	-119.72